WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 233/23, 233/14, 233/41
C07C 275/32, C07D 311/68
C07D 213/40, C07C 231/02
A61K 31/165

A1

(11) International Publication Number: **WO 92/18462**

(43) International Publication Date: 29 October 1992 (29.10.92)

(21) International Application Number: PCT/US92/02662

(22) International Filing Date: 9 April 1992 (09.04.92)

(30) Priority data:
684,623 12 April 1991 (12.04.91) US

(60) Parent Application or Grant
(63) Related by Continuation
US 684,623 (CIP)
Filed on 12 April 1991 (12.04.91)

(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : CLADER, John, W. [US/US]; 428 North Union Avenue, Cranford, NJ 07016 (US). FEVIG, Thomas [US/US]; 7253 Mallard Drive, West Chester, OH 45069 (US). VACCARO, Wayne [US/US]; 1706 Westover Road, Yardley, Pennsylvania 19067 (US). BERGER, Joel, G. [US/US]; 50 W. Lindsley Road #54, Cedar Grove, NJ 07009 (US).

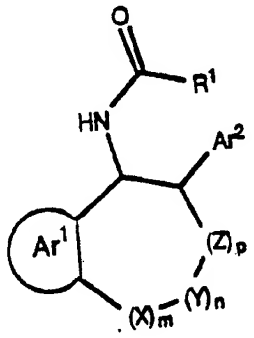
(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, One Giralda Farms, Madison, NJ 07940-1000 (US).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: BICYCLIC AMIDES AS INHIBITORS OF ACYL-COENZYME A: CHOLESTEROL ACYL TRANSFERASE

(I)



(57) Abstract

Novel bicyclic amides of formula (I), wherein Ar^1 and Ar^2 are phenyl, R^2-substituted phenyl, heteroaryl or R^2-substituted heteroaryl, wherein R^2 is 1 to 3 substituents independentlyselected from the group consisting of halogeno, hydroxy, lower alkyl, lower alkoxy, nitro, amino, lower alkylamino and lower dialkylamino; X, Y and Z are $-CH_2-$, -CH(alkyl)-, $-C(alkyl)_2-$, -NH-, -N(alkyl)-, -O- or $-SO_r-$, wherein r is 0, 1 or 2, and m, n and p are 0 or 1; R^1 is an alkyl chain of 1 to 25 carbon atoms; an alkyl chain substituted by one or more optionally substituted phenyl or heteroaryl groups; an alkyl chain -0-, $-S0_r-$, phenylene, R^2-substituted phenylene, heteroarylene or R^2-substituted heteroarylene groups; an interrupted alkyl chain substituted by one or more optionally substituted phenyl or heteroaryl groups; an alkyl chain of 4 to 25 carbon atoms, interrupted by one or more -NH-, -C(O)- or -N(lower alkyl)- groups; an interrupted alkyl chain of 4 to 25 carbon atoms substituted by one or more phenyl, R^2-substituted phenyl, heteroaryl or R^2-substituted heteroaryl groups; a diphenylamino group; a di-(R^2-substituted phenyl)amino group; a diheteroarylamino group ; or a di-(R^2-substituted heteroaryl)amino group; or a pharmaceutically acceptable salt thereof, useful in the treatmeent of artherosclerosis are disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland			SE	Sweden
CI	Côte d'Ivoire	KR	Republic of Korea	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
DE	Germany	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America

BICYCLIC AMIDES AS INHIBITORS OF ACYL-COENZYME A: CHOLESTEROL ACYL TRANSFERASE

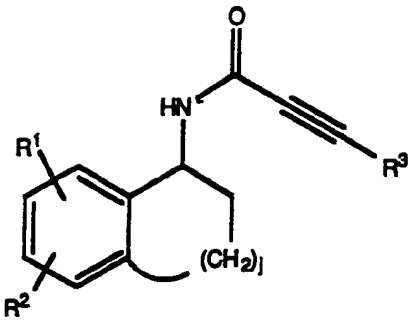
BACKGROUND OF THE INVENTION

The present invention relates to bicyclic amides and to pharmaceutical compositions containing such compounds, for use in the treatment and prevention of atherosclerosis.

Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male sex, cigarette smoking and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk.

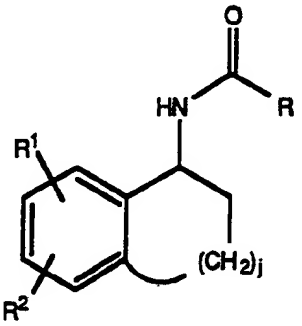
Cholesterol esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesterol esters is also a key step in the intestinal absorption of dietary cholesterol. The intracellular esterification of cholesterol is catalyzed by the enzyme acyl CoA:cholesterol acyl transferase (ACAT, EC 2.3.1.26).. Thus, inhibition of ACAT is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesterol esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A number of bicyclic amides have been reported as being useful in lowering cholesterol and/or inhibiting formation of cholesterol-containing lesions in mammalian arterial walls. U.S. 4,456,619 to Kathawala discloses compounds of the formula



wherein R^1 and R^2 are independently H, lower alkyl, lower alkoxy or halo; j is an integer of from 1 to 3; and R^3 is an alkyl chain of 1 to 23 carbon atoms, saturated or unsaturated, or an alkyl chain as defined wherein each unsaturated ethylenic group is replaced by a cyclopropanyl group.

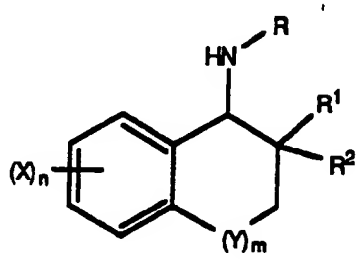
U.S. 4,248,893 to Kathawala et al discloses compounds of formula



wherein j is an integer of from 1 to 3; R^1 and R^2 are independently H, halo, lower alkyl or lower alkoxy; and -C(O)-R is a 7-23 C unsaturated fatty acid radical in which each ethylenic group is replaced by a cyclopropanyl group.

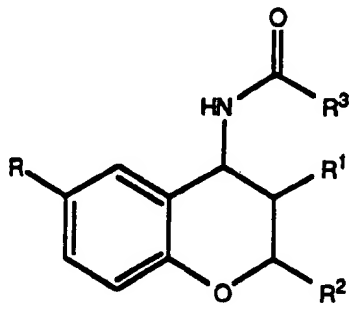
While some of these bicyclic amides have shown in vitro ACAT inhibitory activity, none have been reported to show significant activity in whole animal models of atherosclerosis.

In addition, U.S. 3,704,323 to Krapcho discloses CNS stimulant 2-methyl-2-phenylindanamines of the formula



wherein X is H, OH, lower alkyl, halogen, lower alkoxy, amino or dialkylamino; Y is $-CH_2-$, $-CH_2CH_2-$, -O- or -S-; n is 1, 2 or 3; m is 0 or 1; R^1 is phenyl, pyridyl, or X-substituted phenyl or pyridyl; R^2 is lower alkyl or X-substituted aryl; and R is lower alkyl or hydroxy- or phenyl-substituted lower alkyl.

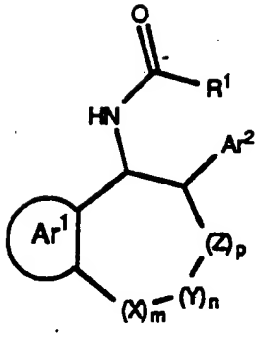
European Patent Application 250,077 to Evans et al discloses hypotensive compounds of the formula



wherein R is alkyl; R^1 is alkoxy or acyloxy; R^2 is lower alkyl; and R^3 is lower alkyl, aryl or heteroaryl.

SUMMARY OF THE INVENTION

Novel compounds of the present invention which show significant in vivo anti-atherosclerotic activity are represented by the formula



I

wherein Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl or R^2-substituted heteroaryl, wherein R^2 is 1 to 3 substituents independently selected from the group consisting of halogeno, hydroxy, lower alkyl, lower alkoxy, nitro, amino, lower alkylamino and lower dialkylamino;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(alkyl)-, $-C(alkyl)_2-$, -NH-, -N(alkyl)-, -O- and $-SO_r-$, wherein r is 0, 1 or 2, and m, n and p are 0 or 1, such that $0< (m+n+p) <4$, provided that only one of X,Y or Z is -NH-, -N(alkyl)-, -O- or $-SO_r-$;

R^1 is an alkyl chain of 1 to 25 carbon atoms, branched or straight, saturated or containing one or more double bonds; an alkyl chain of 1 to 25 carbon atoms as defined substituted by one or more substituents selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl and R^2-substituted heteroaryl; an alkyl chain of 1 to 25 carbon atoms as defined interrupted by one or more Q groups, wherein Q is independently selected from the group consisting of -O-, $-SO_r-$, phenylene, R^2-substituted phenylene, heteroarylene and R^2-substituted heteroarylene; an interrupted alkyl chain of 1 to 25 carbon atoms as defined substituted by one or more substituents selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl and R^2-substituted heteroaryl; an alkyl chain of 4 to 25 carbon atoms, interrupted by one or more groups selected from the group consisting of Q, -NH-, -C(O)- and -N(lower alkyl)-; an interrupted alkyl chain of 4 to 25 carbon atoms as defined substituted by one or more substituents

selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl and R^2-substituted heteroaryl; a diphenylamino group; a di-(R^2-substituted phenyl)amino group; a diheteroarylamino group; or a di-(R^2-substituted heteroaryl)amino group;

or a pharmaceutically acceptable salt thereof.

Preferred are compounds of formula I wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a 6-C ring; Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, lower alkoxy-substituted phenyl, amino-substituted phenyl, hydroxy-substituted phenyl or pyridyl.

Another group of preferred compounds is that wherein one of X, Y or Z is an oxygen atom and $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a six membered ring containing one oxygen atom, and Ar^1 and Ar^2 are both phenyl.

Also preferred are compounds wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a 7-C ring, and Ar^1 and Ar^2 are independently selected from the group consisting of lower alkoxy-substituted phenyl or hydroxy-substituted phenyl.

Yet another group of preferred compounds is that wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbon to which they are attached, form a 5-C ring, and Ar^1 and Ar^2 are independently chosen from the group consisting of phenyl, nitro-substituted phenyl, amino-substituted phenyl, lower alkoxy-substituted phenyl and hydroxy-substituted phenyl.

Still another group of preferred compounds is that wherein R^1 is 1,1-dimethyldecanyl (i.e. $-C(O)R^1$ is 2,2-dimethylundecanoyl); $CH_3(CH_2)_7CH=CH(CH_2)_7-$(i.e. $-C(O)R^1$ is oleoyl); diphenylamino; or a diphenyl substituted alkyl chain, especially diphenylmethyl (i.e.$-C(O)R^1$ is diphenylacetyl).

Especially preferred are compounds of formula I wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a 5-C ring; Ar^1 is phenyl; Ar^2 is hydroxy-substituted phenyl and R^1 is diphenylmethyl.

This invention also relates to the use of the ACAT inhibitors of the present invention as hypolipidemic and hypocholesterolemic agents in mammals.

In another aspect, the invention relates to pharmaceutical compositions comprising an ACAT inhibitor of the present invention in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

Generally accepted abbreviations are used throughout the specification and claims to identify solvents and reagents as follows: N,N-dimethylformamide (DMF); 1-hydroxy-benzotriazole (HOBT); tetrahydrofuran (THF); dicyclohexylcarbodiimide (DCC); 1-(3'-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI); methanol (MeOH); ethyl acetate (EtOAc); diisobutylaluminum hydride (DIBAL-H); N-bromosuccinimide (NBS); palladium on carbon (Pd/C); triethylamine (Et_3N); N,N-dimethylaminopyridine (DMAP); N-methylmorpholine (NMM); p-toluenesulfonic acid (pTSA); hydrochloric acid (HCl); triphenylphosphine (Ph_3P); diethylazodicarboxylate (DEAD); ethanol (EtOH); ethanethiol (EtSH); sodium acetate (NaOAc); glacial acetic acid (HOAc); diethyl ether (ether).

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms and "lower alkoxy" similarly refers to alkoxy groups having 1 to 6 carbon atoms.

Halogeno refers to fluorine, chlorine, bromine or iodine radicals.

"Phenylene" means a bivalent phenyl group, including ortho, meta and para-substitution and "heteroarylene" similarly means a bivalent heteroaryl group.

Heteroaryl means an aromatic group having 5 or 6 ring members wherein 1-3 ring members are independently selected from the group consisting of nitrogen, oxygen and sulfur. Examples of heteroaryl groups are pyridyl, pyrimidinyl, pyrazinyl, triazinyl, pyrrolyl, furanyl and thienyl.

The alkyl chain as defined in R^1 can be a radical of a synthetic or natural fatty acid, either saturated or containing one or more carbon to carbon double bonds, or can be an interrupted alkyl chain wherein one or more of the carbon atoms in the chain can be replaced by an -O-, -SO_r-, phenylene or heteroarylene group; and when the alkyl chain is greater than 4 carbons in length it can be additionally interrupted by -NH-, -N(lower alkyl)-, or -C(O)- group. When substituted by optionally substituted phenyl or heteroaryl groups, the alkyl chain or interrupted alkyl chain may be independently substituted on different carbon atoms, di-substituted on one carbon atom, or both.

One skilled in the art will recognize that the number of double bonds present, the replacement of carbon atoms in the chain and the presence of substituents on the carbon atoms in the chain are all dependent on the length of the chain: shorter alkyl chains cannot accommodate as many bonds, carbon replacements or substituents as longer alkyl chains. In general, unsaturated alkyl chains contain 1 to 4 double bonds, conjugated or non-conjugated. Where carbon atoms are replaced, 1 to 4 replacement groups can be present. Similarly, when carbon atoms in the chain are substituted, 1 to 4 substituents can be present.

Examples of alkyl chains are as follows, wherein the group -C(O)R^1 is named: palmitoyl, stearoyl and 2,2-dimethyldodecanoyl.

Examples of unsaturated -C(O)R^1 groups are oleoyl, linoleoyl, linolenoyl, elaidoyl, eicosatetraenoyl, eicosapentaenoyl and arachidonoyl.

Examples of -C(O)R^1 groups wherein the carbon atoms are substituted are diphenylacetyl, 3,3-diphenylpropionyl and 2,3-diphenylpropionyl.

Examples of -C(O)R^1 groups wherein carbon atoms in the chain are replaced are: 3-methoxy-4-(tetradecyloxy)-benzoyl, 11-[N-(2,2-diphenylacetyl)amino]undecanoyl and phenoxyundecanoyl.

An example of a di-substituted amino -C(O)R^1 group is N,N-diphenylaminocarbonyl.

Compounds of the invention have at least two asymmetrical carbon atoms and therefore include rotational isomers. The invention includes all possible stereoisomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials or by separating isomers of a compound of formula I.

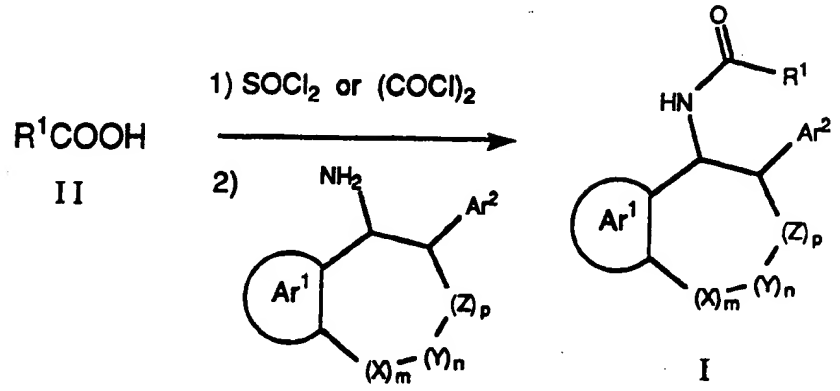
Isomers may include geometric isomers, e.g. when R^1 contains a double bond. All such isomers are contemplated for this invention.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a phenol or carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Compounds of formula I can be prepared under standard reaction conditions well known in the art. For example, a carboxylic acid of formula II can be converted to the acid chloride by treatment with thionyl or oxalyl chloride in a solvent such as CH_2Cl_2, then reacted with

an amine of formula III in the presence of a tertiary amine base such as Et_3N, DMAP or NMM:



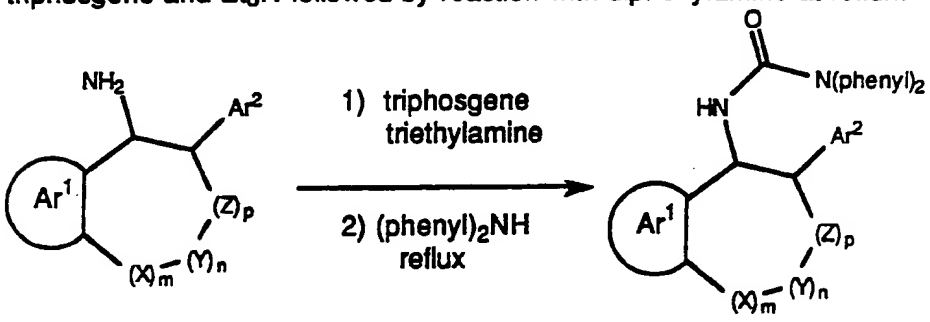
Alternatively, the acid of formula II and the amine of formula III can be reacted in the presence of a coupling agent such as DCC or EDCI and a base such as Et_3N, DMAP or NMM in a solvent such as CH_2Cl_2 or THF at a temperature of 0°C to 23°C. In a third method, the carboxy group of acid II can be activated via the intermediacy of an active ester such as that derived from HOBT.

Starting compounds of formula II are commercially available or can be prepared by well known methods.

Compounds of formula Ib, wherein one of Ar^1 or Ar^2 is R^2-substituted phenyl and R^2 is hydroxy, can be prepared by treating a compound of formula Ia, wherein one of Ar^1 or Ar^2 is R^2-substituted phenyl and R^2 is methoxy, with BBr_3. In an alternative method, a compound of formula Ia can be added to a mixture of NaH and EtSH in DMF and heated at reflux to prepare a compound of formula Ib.

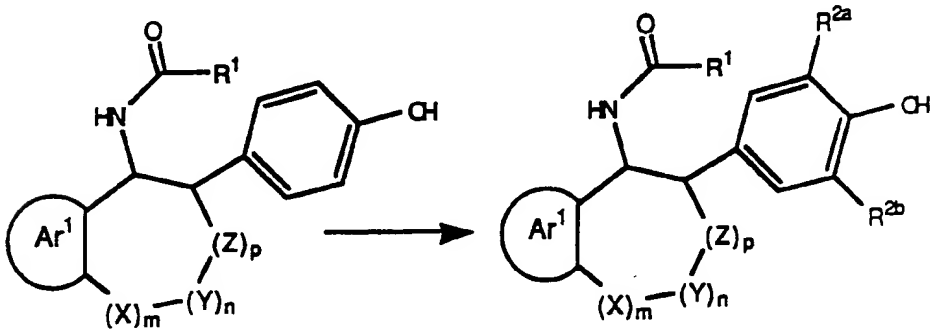
Compounds of formula Id, wherein one of Ar^1 or Ar^2 is R^2-substituted phenyl and R^2 is a primary amino group, can be prepared by hydrogenation over a suitable catalyst, e.g.5% Pd/C, of a compound of formula Ic, wherein one of Ar^1 or Ar^2 is R^2-substituted phenyl and R^2 is a nitro group.

Compounds of formula If, wherein R^1 is N,N-diphenylamino, can be prepared by treatment of an amine of formula III with triphosgene and Et_3N followed by reaction with diphenylamine at reflux:



III If

Compounds of the formula Ig, wherein R^{2a} and R^{2b} are independently hydrogen, bromo, chloro or methyl, can be prepared from a compound of formula Ih, i.e., a compound of formula I wherein Ar^2 is 4-hydroxyphenyl, by a variety of methods. In a method for preparing compounds of the formula Ig, wherein one of R^{2a} or R^{2b} is bromo and the other is hydrogen, a compound of the formula Ih is treated with a suitable brominating agent, e.g. NBS, in dry DMF.



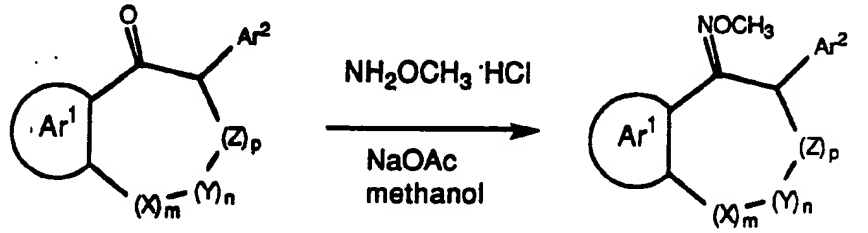
Ih Ig

Compounds of the formula Ig, wherein R^{2a} and R^{2b} are independently hydrogen or chloro, can be prepared by treating a compound of the formula Ih with an appropriate quantity of a suitable

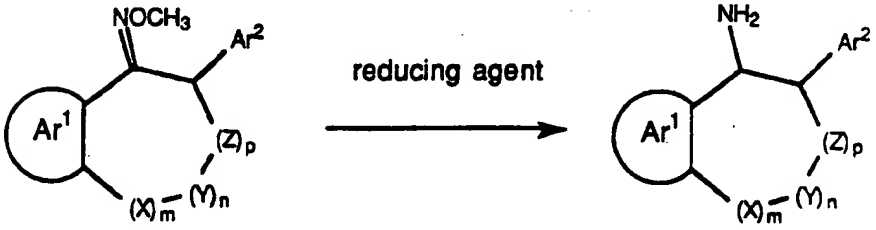
chlorinating agent, e.g. sulfuryl chloride, in dry organic solvent, e.g. a mixture of CH_2Cl_2 and ether.

A method for preparing a compound of the formula Ig, wherein R^{2a} and R^{2b} are independently hydrogen or methyl comprises treating a compound of the formula Ih with formaldehyde, 10% aqueous KOH in DMF and heating the mixture followed by hydrogenation of the product so obtained at elevated pressure, e.g. 60 psi hydrogen, with a suitable catalyst, e.g. 20% $Pd(OH)_2$ on carbon, and using an appropriate solvent, e.g. HOAc.

Amines of formula III can be prepared by several methods. In one method, a ketone of formula IV is reacted with methoxylamine hydrochloride and NaOAc in a solvent such as MeOH to obtain an oxime methyl ether of formula V. The oxime ether is reduced to the desired amine III (as a mixture of cis and trans isomers), by treatment with a suitable reducing agent such as borane or alternatively by reduction with hydrogen gas at 50 psi in the presence of a suitable catalyst such as 10% Pd/C:

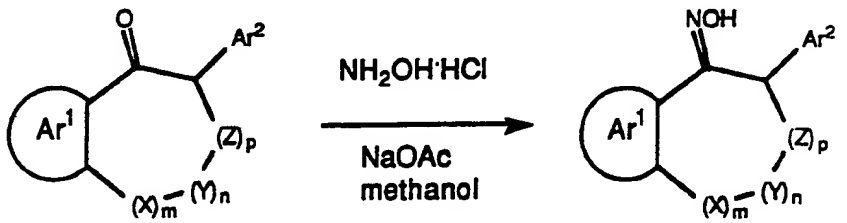


IV V

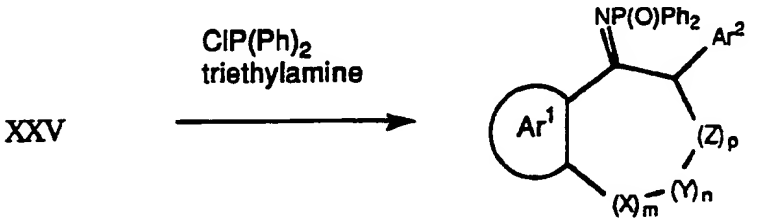


V III

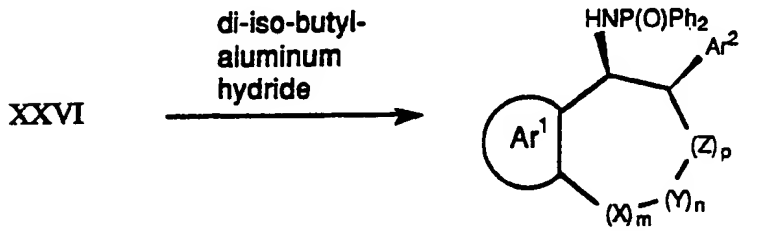
In a method of preparing a cis-amine of formula III-cis, a ketone of formula IV is converted to an oxime of formula XXV by treatment with hydroxylamine hydrochloride and NaOAc in MeOH. The oxime XXV is treated with chlorodiphenylphosphine and Et_3N to form a phosphinylimine XXVI. Reduction of the phosphinylimine to a cis-phosphonamide XXVII with DIBAL-H followed by hydrolysis with HCl in MeOH forms the desired cis-amine:



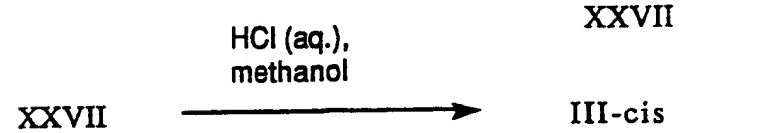
IV XXV



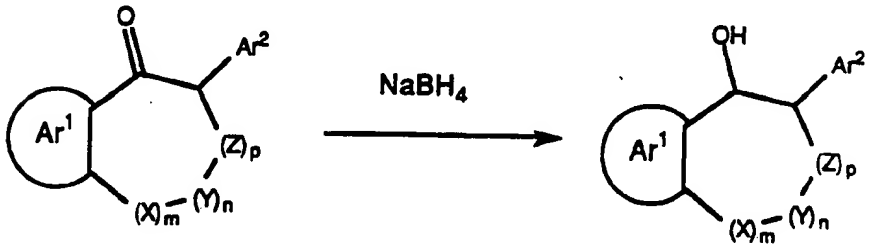
XXVI



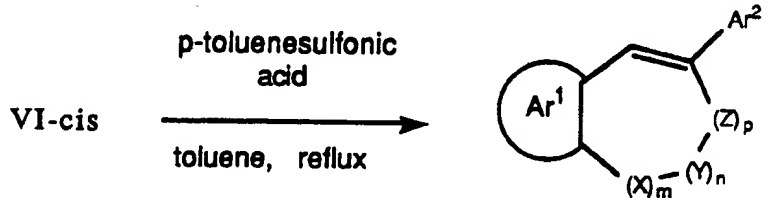
XXVII



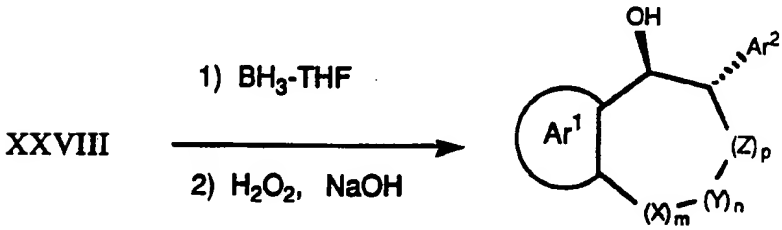
A second method of preparing a cis-amine of formula III-cis involves reducing a ketone of formula IV with $NaBH_4$. The resulting alcohol VI is dehydrated by treating with pTSA in refluxing toluene to form an olefin XXVIII. The olefin is reacted with borane-THF complex then oxidized with H_2O_2 and base to produce the trans-alcohol VI-trans. The trans-alcohol is converted to the corresponding cis-azide VII-cis by reaction with diphenylphosphoryl azide, DEAD and Ph_3P. Reduction of the azide to the desired amine III-cis is accomplished by reaction with hydrogen gas at 50-60 psi in the presence of a suitable catalyst such as 10% Pd/C:



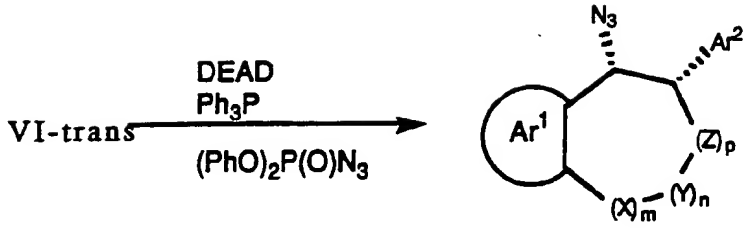
IV VI



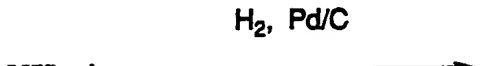
XXVIII



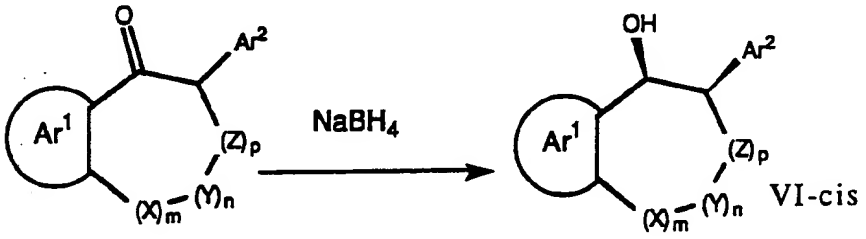
VI-trans



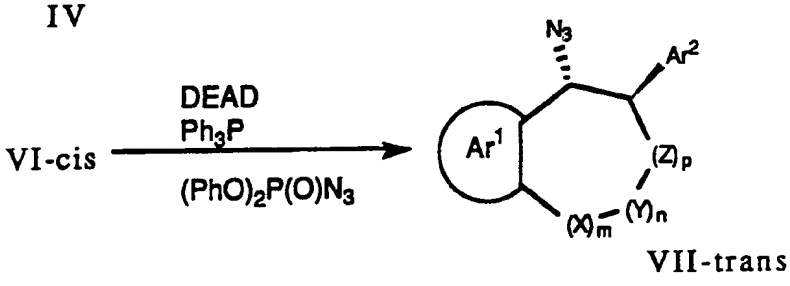
VII-cis



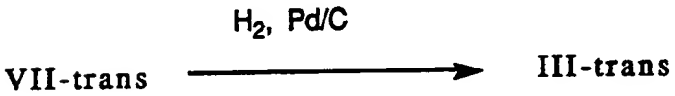
A method for preparing a trans-amine of formula III-trans involves reducing a ketone of formula IV to a cis-alcohol of formula VI-cis using a suitable reducing agent, such as DIBAL-H. The alcohol VI-cis is converted to the desired trans-amine via the trans-azide VII-trans as described above for VI-trans:



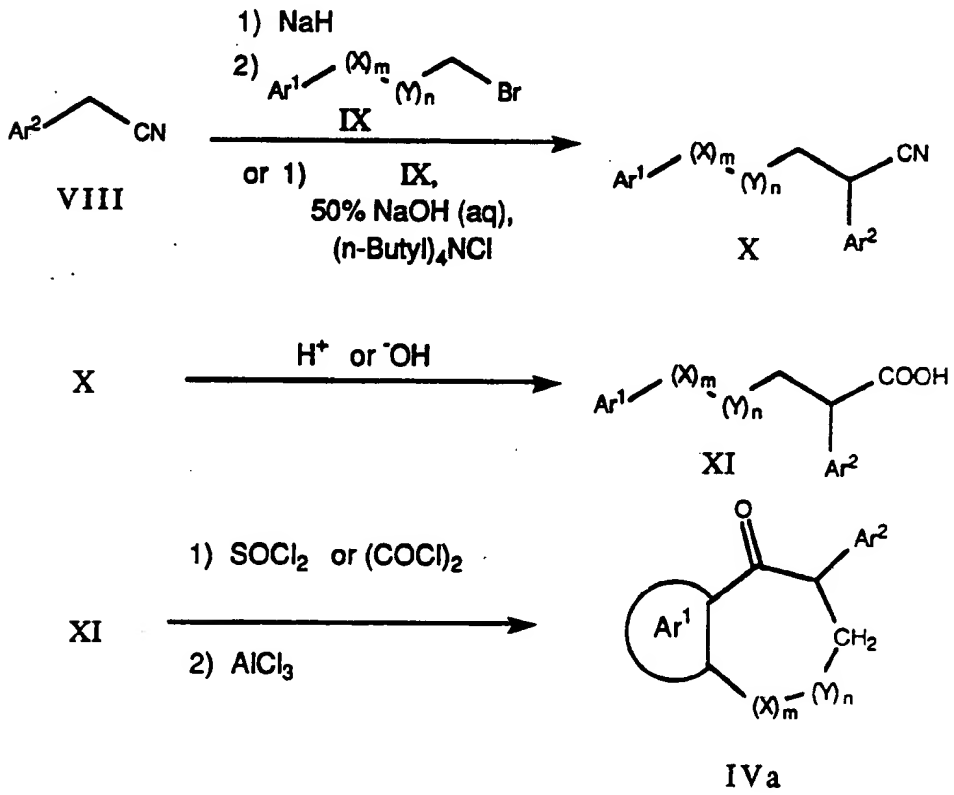
IV



VII-trans



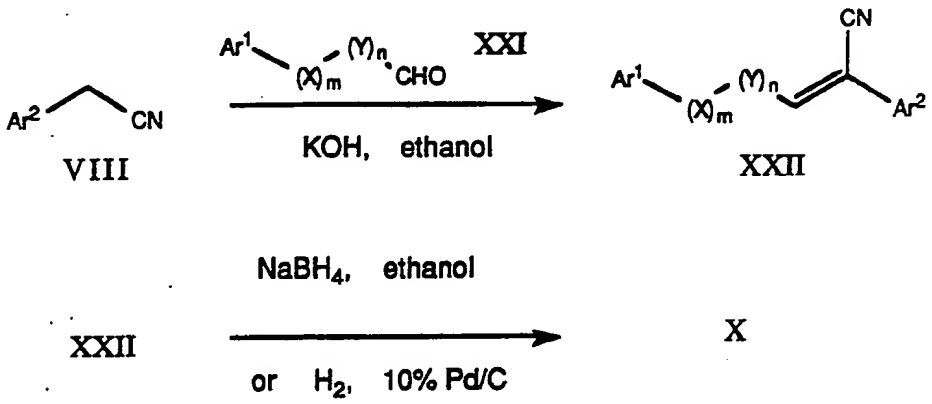
Ketones of formula IV can be prepared by several methods. In a method for preparing a ketone of formula IVa, wherein Z is $-CH_2-$ and p is 1, a nitrile of formula VIII is treated with a suitable base, such as NaH, then reacted with a halide of formula IX to form a nitrile of formula X. Alternatively, the nitrile VIII is treated with the halide IX and 50% sodium hydroxide (aqueous) in the presence of a suitable phase transfer catalyst such as tetra-n-butylammonium chloride to form the nitrile X. The nitrile X is subjected to hydrolysis under either acidic or basic conditions to form a carboxylic acid of formula XI. The acid of formula XI can be converted to the acid chloride by treatment with thionyl or oxalyl chloride in a solvent such as CH_2Cl_2, then treated with a Lewis acid, such as anhydrous $AlCl_3$, to form the ketone IVa:



Alternatively, a nitrile of formula X can be combined with NaCl and $AlCl_3$, then heated to 180°C, followed by hydrolysis to directly form the ketone IVa.

Starting nitriles of formula VIII and halides of formula IX are commercially available or can be prepared by well known methods.

In a second method of preparing ketones of formula IVa, a nitrile of formula VIII is condensed with an aldehyde of formula XXI under basic conditions to form an unsaturated nitrile of formula XXII. The unsaturated nitrile of formula XXII is reduced using $NaBH_4$ in EtOH to a nitrile of formula X which is converted to a ketone of formula IVa as described above:

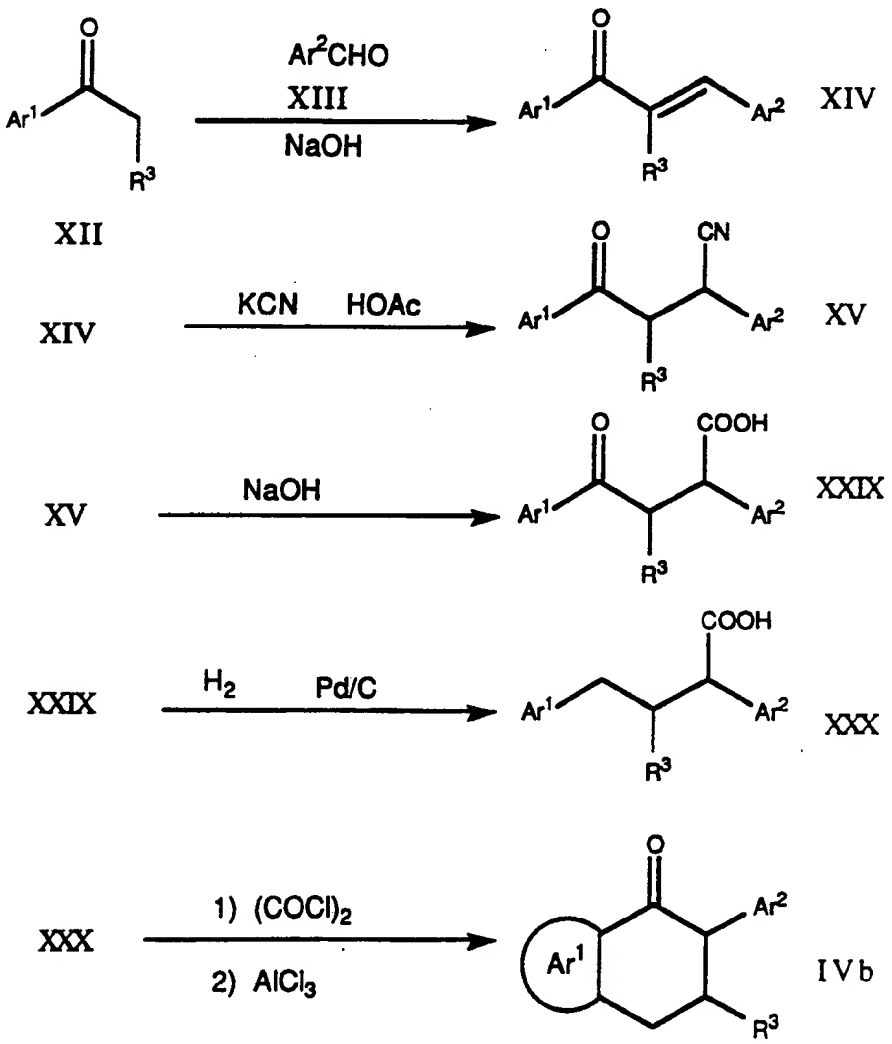


Alternatively, the unsaturated nitrile XXII can be reduced by hydrogenation at 50 psi of hydrogen in the presence of a suitable catalyst such as 10% Pd/C.

Starting aldehydes of formula XXI and nitriles of formula VIII are commercially available or can be prepared by methods well known to those skilled in the art.

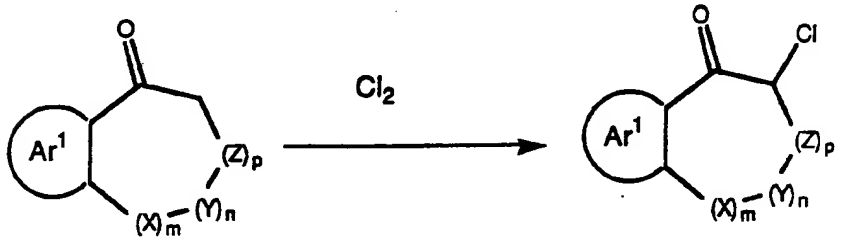
In a method of preparing a ketone of formula IVb, wherein R^3 is H or alkyl and $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, comprise a 6-C ring, a ketone of formula XII is condensed with an aldehyde of formula XIII under basic conditions to form a ketone of the formula XIV. The ketone of formula XIV is reacted with potassium cyanide and HOAc to form a ketonitrile of formula XV.

Hydrolysis of the nitrile XV gives the keto-acid XXIX which is reduced with hydrogen gas at 50 psi in the presence of a suitable catalyst such as 10% Pd/C to a carboxylic acid of formula XXX. The acid of formula XXX can be converted to a ketone of the formula IVb via the process described above for XI:

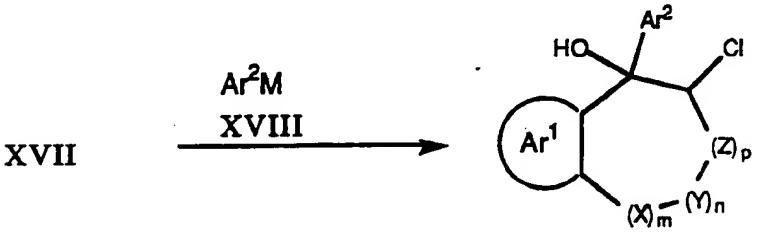


Starting ketones of formula XII and aldehydes of formula XIII are commercially available or can be prepared by well known methods.

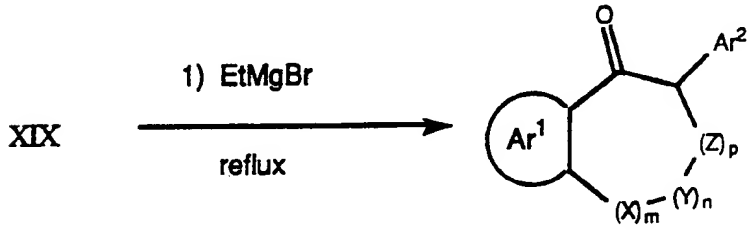
A ketone of formula IV can be prepared by treatment of a ketone of formula XVI with chlorine to form an α-chloro-ketone of formula XVII. Treatment of the chloroketone XVII with an organometallic reagent of formula XVIII, wherein M is Li, Ce or MgBr produces an alcohol of formula XIX. Reaction of the alcohol XIX with ethylgrignard reagent in a suitable solvent such as THF at reflux temperature forms the desired ketone IV:



XVI XVII



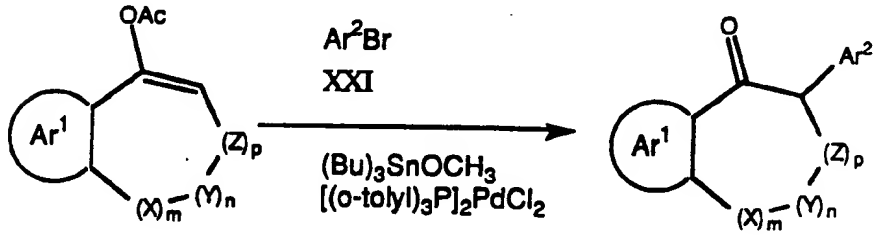
XIX



IV

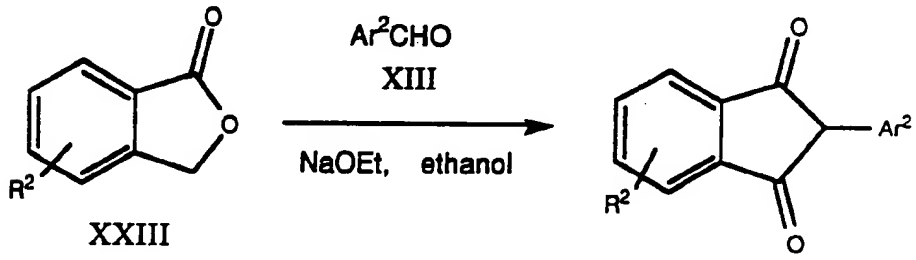
Starting ketones of formula XVI and organometallic reagents of formula XVIII are commercially available or can readily be prepared via procedures well known to those skilled in the art.

Another method of preparing a ketone of formula IV involves reacting an enol acetate of formula XX with an aryl halide of formula XXI and tri-n-butyltin methoxide in the presence of a suitable catalyst such as $[(ortho\text{-}tolyl)_3P]_2PdCl_2$:

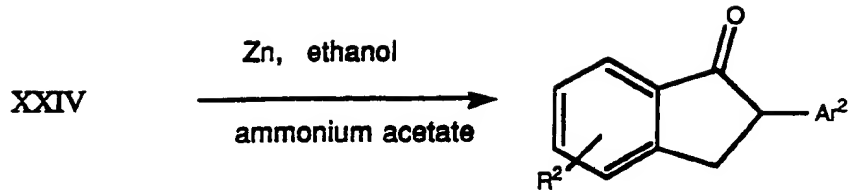


XX IV

In a method for preparing ketones of formula IVc, wherein Ar^1 is R^2-substituted phenyl; and $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, comprise a 5-C ring, an aldehyde of formula XIII and a lactone of formula XXIII are treated with sodium ethoxide in EtOH at reflux to form an indanedione of formula XXIV. The indanedione of formula XXIV is treated with NH_4OAc in EtOH at reflux, then reduced with zinc dust to form the desired ketone IVc:



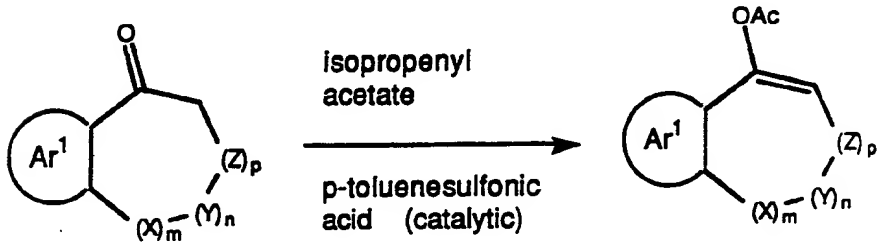
XXIII XXIV



IVc

Starting lactones of formula XXIII and aldehydes of formula XIII are commercially available or can be prepared by methods well known to those skilled in the art.

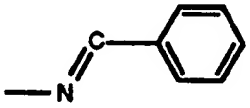
Enol acetates of formula XX can be prepared by reacting a ketone of formula XVI with isopropenyl acetate in the presence of a catalytic amount of a suitable acid, such as pTSA.



XVI XX

Starting ketones of formula XVI are commercially available or readily prepared by well known methods.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following table shows some typical protecting groups:

Group to be protected	Protected group
—OH	—OCH_3
—NH_2	
—COOH	-COOalkyl, -COObenzyl, -COOphenyl

We have found that the compounds of this invention are inhibitors of ACAT in vitro and in whole animal models the compounds have been found to significantly reduce the formation of liver cholesterol esters. Thus, compounds of this invention are hypocholesterolemic and hypolipidemic agents by virtue of their ability to inhibit the esterification and intestinal absorption of cholesterol; they are therefore useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

In addition to the compound aspect, the present invention therefore also relates to a method of treating atherosclerosis, in particular by reducing serum cholesterol, which method comprises administering to a mammal in need of such treatment a hypocholesterolemic effective amount of a compound of this invention. The compound is preferably administered in a pharmaceutically acceptable carrier suitable for oral administration.

The in vitro and in vivo activity of the present compounds can be determined by the following procedures.

ACAT Assay (In vitro)

This assay measures the activity of ACAT by measuring the ACAT-mediated transfer of tritiated oleic acid from acyl-CoA to

cholesterol to give labelled cholesterol oleate. Rat liver microsomes are used as the source of ACAT. Assays are performed in round bottom microtiterplates using a total incubation volume of 50 µL. Each incubation well receives 10 µL assay buffer (0.5M $KHPO_4$, 10 µM dithiothreitol, pH 7.4), 7.5 µL of 40 mg/mL BSA (Bovine Serum Albumin) and 12.5 µg of microsomal protein. The test compound (in sufficient amount to bring the final concentration to from 0.1 to 25 µM), reference compound, or vehicle control is added and the final volume brought to 47 µL. The microtiterplate is then floated on the surface of a 37°C water bath for fifteen minutes. Incubations are started by the addition of 3 µL ^{3}H-acyl CoA (1µCi/well, final concentration of 10 µM acyl CoA). The plate is then returned to the water bath for 15 minutes. The incubations are then terminated by application of 15 µL from each incubation to individual lanes on a thin layer plate (Silica Gel GF 20 x 20 cm). Standards are applied to several lanes so that the cholesterol ester band can be identified. After drying, the plates are eluted with 90:10:1 petroleum ether:ether:HOAc. The standards are visualized via iodine vapor, and the regions corresponding to cholesterol ester are scraped into 7 mL scintillation vials. 4 mL of scintillant are added to each vial, and the radioactivity quantified. Background count is determined by the boiled controls. Full activity is determined by activity in the presence of vehicle. The percent inhibition is calculated by subtracting the background from both control and test samples, and the test value is calculated as a percentage of the control. For IC_{50} determinations, the inhibition is plotted against drug doses on a log scale and the concentration at which 50% inhibition is obtained is determined.

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a control cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the

initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by IM injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of this invention and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional oral dosage form such as capsules, tablets, powders, cachets, suspensions or solutions. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrates, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesterolemic or hypolipidemic dose of a compound of formula I is about 7 to about 30 mg/kg of body weight per day. For an average body weight of 70 kg, the dosage level is therefore from about 500 to about 2000 mg of drug per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight condition and response of the patient.

Following are preparations of starting materials and examples of preparing compounds of formula I.

Preparation 1: 2-(4'-methoxyphenyl)-1-indanone

Step A Dissolve benzaldehyde (489 mL, 4.816 mol) and p-methoxyphenylacetonitrile (598 mL, 4.414 mol) in 95% EtOH (1.5 L). Stir the solution at room temperature while adding 40% aqueous KOH (489 g, 8.732 mol, in 863 mL water) in 2.2 L of 95% EtOH. Stir the

mixture for an additional 1.5 h at room temperature, then collect the crystals by suction filtration, wash with water and cold 95% EtOH, and air dry. The weight of the white, crystalline product (mp 92-94°C., lit. 112°C.) is 999.4 g (96.3%).

Step B Suspend the product of step A (16.01 g, 68.13 mmol) in absolute EtOH (200 mL) at 60-70°C under N_2. Add solid $NaBH_4$ (2.589 g, 68.13 mmol) in portions over 10 min, and stir the mixture at the same temperature for 2 h. Cool the reaction mixture to ambient temperature and quench with water. Pour the mixture into a volume of water and acidify with conc. HCl. Extract the product into two portions of ether. Combine the organic layers, wash with water and brine, then dry over anhydrous Na_2SO_4. Filter the product solution and evaporate to give the crude product (15.88 g, 98.4%), mp 66-67°C.(lit. 104°C.), which can be used without further purification. Alternatively, isolate the product by diluting the crude reaction mixture with several volumes of water, and collect the resulting precipitate by suction filtration (99%).

Step C Combine the product of step B (932.8 g, 3.94 mol) and ethylene glycol (9 L), add a solution of KOH (673 g, 12.02 mol) in water (2.1 L), and heat the mixture at reflux overnight (internal temperature: 120°C). Cool the reaction mixture, pour into water, and extract twice with diethyl ether. Acidify the aqueous phase with conc. HCl and extract with two portions of ether. Combine the latter organic extracts, wash with brine, dry over Na_2SO_4, filter and evaporate. Dissolve the crude product in CH_2Cl_2 and dilute with hexane to induce crystallization. Collect the crystals by suction filtration, wash with hexane/EtOAc (5:1) and hexane, and air dry. Yield: 943.8 g (93.7%), mp 107-109°C (lit. 114°C).

Step D Dissolve the product of step C (64.14 g, 0.251 mol) in 400 mL of CH_2Cl_2 in a 1 L flask under N_2. Treat the solution with three drops of DMF, then add oxalyl chloride (55 mL, 0.626 mol), via syringe. Stir the mixture overnight at room temperature, evaporate, dilute with dry CH_2Cl_2, and evaporate again. Dissolve the residue in dry CH_2Cl_2 (100 mL) and add the solution, via dropping funnel (over 5 h), to

a suspension of $AlCl_3$ in dry, ice cold CH_2Cl_2 (800 mL) under N_2. Following the addition, stir the mixture for 15 min at 0°C, then pour into water and extract three times with ether. Combine the organic layers, wash successively with water, dilute K_2CO_3 solution, and brine, then dry over Na_2SO_4. Filter the product solution and evaporate, then crystallize the resulting residue from EtOH (3 mL/g) to give the title compound (51.3 g, 86%), mp 83-85°C (lit. 79-81°C).

Using a similar procedure, the following compounds can also be prepared: 2-(3'-nitrophenyl)indanone, mp 115-118°C; 2-(4'-nitrophenyl)indanone, mp 145-148°C; and 2-phenyl-5-methoxy-indanone, ms 238 (100).

Preparation 2: 2-(4'-methoxyphenyl)-1,2,3,4-tetrahydro-naphthalen-1-one

Step A Add 10% aqueous NaOH (38 mL) to a solution of p-anisaldehyde (25 mL, 0.206 mol) and acetophenone (23.97 mL, 0.206 mol) in EtOH (500 mL). Stir the mixture at room temperature over night. Dilute the mixture with water and extract with ether. Combine the ethereal extracts, wash with water and brine, dry over Na_2SO_4 and concentrate to a solid. Recrystallize the solid from ether/hexanes to provide 27.51 g (56%) of 4'-methoxychalcone, mp 72-74°C.

Step B Add KCN (11.27 g, 0.173 mol) in water (25 mL) to a 100 °C solution of 4'-methoxychalcone (27.51 g 0.115 mol) and HOAc (7.5 mL, 0.128 mol) in 2-methoxyethanol (200 mL). The reaction is complete in <10 min. Cool the resulting solution to room temperature and pour into a mixture of ice and water (1 L). Extract the mixture with EtOAc. Combine the organic extracts, wash with water and brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Recrystallize the resulting solid from CH_2Cl_2/MeOH to provide 23.07 g (75%) of 2-(4'-methoxyphenyl)-4-phenyl-3-oxobutyronitrile, mp 115-116°C.

Step C Add a solution of NaOH (34.56 g, 863.9 mmol) in water (375 mL) to a solution of 2-(4'-methoxyphenyl)-4-phenyl-4-oxo-butyronitrile (22.92 g, 86.39 mmol) in EtOH (160 mL). Heat the resulting

mixture to reflux under nitrogen and monitor the progress of the hydrolysis by TLC (30% EtOAc/hexane, Ce stain). When all of the starting nitrile is consumed, after ~ 5h, cool the reaction to room temperature. Dilute the solution with water(1 L), and stir while acidifying with 10% aqueous HCl (pH ~1-2). Collect the resulting precipitate via vacuum filtration, wash with water and air dry to provide 39.43 g of a solid. Dissolve most of the solid in a mixture of CH_2Cl_2/ MeOH/EtOAc. Vacuum filter through celite, then concentrate the filtrate to a solid and recrystallize from CH_2Cl_2/hexanes to provide 18.27 g (74.4%) of 2-(4'-methoxyphenyl)-4-phenyl-4-oxo-butyric acid, mp 157-158°C.

Step D Dissolve 2-(4'-methoxyphenyl)-4-phenyl-4-oxobutyric acid (18.07 g, 63.55 mmol) in a mixture of MeOH (~25 mL) and HOAc (125 mL). Purge the resulting solution with nitrogen. Add 10% Pd/C (2 g) and hydrogenate on a Parr apparatus over night at ~55 psi. Vacuum filter the mixture through celite. Thoroughly wash the filter cake with 25% MeOH/ CH_2Cl_2 (300 mL). Concentrate the filtrate *in vacuo* to give 18.08 g of a solid, and recrystallize from ether/hexanes to provide 12.8 g (74.6%) of 2-(4'-methoxyphenyl)-4-phenylbutyric acid, mp 92-97°C.

In a manner similar to that in preparation 1, step D, treat 2-(4'-methoxyphenyl)-4-phenylbutyric acid to obtain the title compound, mp 107-107.5°C.

The following compounds can be prepared using a similar procedure: 2-(2'-methoxyphenyl)-1-tetralone, ms = 253 (M^+1); and 2-(3'-methoxyphenyl)-1-tetralone, mp 86-87°C.

Preparation 3: 2-(3'-methoxyphenyl)-1-indanone

Step A Prepare a solution of sodium ethoxide using sodium (10.12 g, 0.44 mol) and 200 mL of absolute EtOH under N_2. Rapidly add to this solution, a mixture of phthalide (29.5 g, 0.22 mol) and m-anisaldehyde (30 g, 0.22 mol) in 100 mL of EtOH. Heat the reaction mixture to 85°C and stir at this temperature overnight. Cool to room temperature, acidify carefully with concentrated HCl, then add water to

precipitate the product. Collect the precipitate by filtration, wash with water, and air dry to give 34.15 g of the product (61.6%), mp 144-146°C.

Step B Dissolve the product from step A (3.01 g, 11.94 mmol) in EtOH (200 mL) under N_2 and treat with ammonium acetate (17.98 g, 233 mmol). Heat mixture at reflux for 4 h and then cool to room temperature. Add zinc dust (7.5 g, 115 mmol) and heat the mixture at reflux for 2.5 h more. Filter the yellow reaction mixture while hot, and dilute the filtrate with water until cloudy. Allow the filtrate to stand in the freezer overnight. Collect the resulting crystals by filtration, wash successively with cold 6 N HCl and water, and dry to obtain the title compound (1.45 g, 51.0%), mp 144-146 °C.

Preparation 4: 2-phenyl-1,2,3,4-tetrahydronaphthalen-1-one

Step A Bubble chlorine gas through a 0°C solution of 1-tetralone (93 mL, 0.70 mol) in CH_2Cl_2 (500 mL). Closely monitor the reaction by TLC (50% CH_2Cl_2/hexane). When all of the 1-tetralone is consumed, wash the reaction mixture successively with saturated $NaHCO_3$, water and brine, dry over Na_2SO_4 and concentrate to an oil. Dissolve the oil in ether (150 mL) and place in the freezer. Collect the resulting crystals via vacuum filtration and wash with cold hexane. Dry the crystals *in vacuo* to afford 73.26 g of a solid. Chromatograph 10.8 g of the solid on silica gel, using 50% CH_2Cl_2/hexane to elute the column, to obtain 7.51g of 2-chloro-1,2,3,4-tetrahydronaphthalen-1-one. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.09 (1H, d, J= 5.2 Hz); 7.53 (1H, dt, J= 4.9, 0.9 Hz); 7.36 (1H, t, J= 5.2 Hz); 7.28 (1H,d, J= 5.0 Hz); 4.64 (1H,dd, J= 2.6, 5.2 Hz); 3.29 (1H, m); 3.00 (1H, m); 2.59 (1H, m); 2.46 (1H, m).

Step B Dry 1.85 g (7.51 mmol) of finely ground cerium trichloride heptahydrate at 140 °C for 2.5 h under vacuum. Cool to room temperature under N_2 and add THF (10 mL). Stir the resulting suspension for ~20 h, then cool to 0°C and treat with phenylmagnesium bromide (3.76 mL, 7.51 mmol, 2 M in THF). Stir the mixture at 0°C for 1.5h and then cool to -78 °C. Add a -78 °C solution of 0.94 g (5.2 mmol) of 2-chloro-1-tetralone in THF (10 mL) via cannula. Warm th mixture to

0°C and quench the mixture by adding saturated NH_4Cl (aqueous). Add 1 M aqueous HCl to dissolve any residual salts. Extract with ether, combine the ethereal extracts, wash with water and brine, dry over Na_2SO_4 and concentrate to give 1.54 g of an oil. Chromatograph on silica gel (50% CH_2Cl_2/hexane) to provide 1.38 g of 2-chloro-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.23 (9H, m); 4.66 (1H, dd, J= 31., 6.5 Hz); 3.22 (2H, m); 2.92 (1H, dt, J= 5.8, 17.2 Hz); 2.22 (2H, m).

Step C Add ethylmagnesium bromide (1.76 mL, 5.27 mmol, M in) dropwise to a 0°C solution of 2-chloro-1-phenyl-1,2,3,4-tetrahydronaphth-l-ol (1.36 g, 5.27 mmol) in dry benzene (20 mL). Stir the solution at 0°C for 30 min and heat to reflux for 5 hours. Cool the mixture to room temperature and quench with saturated NH_4Cl (aqueous). Extract with ether, combine the ethereal extracts, wash with water and brine, dry over Na_2SO_4 and concentrate to provide 1.1 g (94%) of the title compound. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.10 (1H, d, J= 7.8 Hz); 7.51 (1H, dt, J= 1.6, 7.4 Hz); 7.29 (5H, m); 7.19 (2H, m); 3.80 (1H, t, J= 8 Hz); 3.09 (2H, m); 2.44 (2H, m).

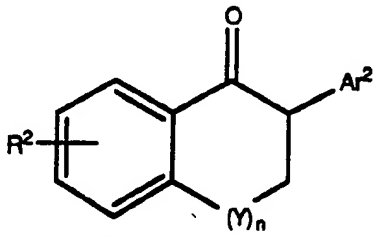
Preparation 5: 2-phenylbenzosuberone

Step A Heat a mixture of benzosuberone (12.34 g, 77.02 mmol), isopropenyl acetate (17.8 mL, 161.7 mmol) and pTSA (0.146 g, 0.77 mmol) at reflux overnight (~20 h). Distill the mixture, discarding the fraction distilling from 60-90°C. Cool the pot residue to room temperature and pour it into a rapidly stirred 1:1 mixture of diethyl ether and aqueous $NaHCO_3$ (saturated). Separate and discard the aqueous layer, then wash the ether layer successively with aqueous $NaHCO_3$ (sat.), water and brine, dry over Na_2SO_4 and concentrate to a solid 15.42 g (99%), mp 58.5-60°C.

Step B Combine the product of step A (30.18 g, 149.2 mmol), tri-n-butyltin methoxide (43 mL, 149.2 mmol), palladium acetate (0.336 g, 1.492 mmol), tri-o-tolylphospine (0.908 g, 2.984 mmol), p-bromoanisole (19 mL, 149.2 mmol) and anhydrous toluene (300 mL), and heat the mixture to 100 °C overnight. Cool to room temperature and

add 5 volumes of EtOAc and 250 mL of 2.5 M KF (aq.). Stir the mixture overnight and vacuum filter. Wash the filtrate with water and brine, dry over Na_2SO_4 and concentrate to an oil. Vacuum distill the oil to remove 23.7 g of unidentified material. Discontinue the distillation when the enolacetate crystallizes in the condenser. Chromatograph the pot residue on silica gel using 10% EtOAc/hexane to obtain 17.89 g (45%) of the title compound, ms = 267 (M^+).

The following compounds can be prepared using a similar procedure:



Compound #	R^2	Ar^2	Y	n	physical data
5A	6-CH_3O	C_6H_5	CH_2	1	mp 116-117°C
5B	H	C_6H_5	O	1	mp 76-77°C
5C	H	4-amino-phenyl	CH_2	1	ms= 237 (M^+)
5D	H	4-CH_3O-phenyl	CH_2	1	mp 107-107.5°C
5E	7-CH_3O	C_6H_5	CH_2	1	mp 74-75°C
5F	5-CH_3O	C_6H_5	CH_2	1	mp 81-82°C
5G	7-CH_3O	4-CH_3O-phenyl	CH_2	1	mp 92-93°C

Preparation 6: 2-(4'-pyridyl)-1,2,3,4-tetrahydro-naphthalen-1-one

Step A Add 30 mL of 50% NaOH (aq.) to a mixture of phenethylbromide (13.23 mL, 97.0 mmol), 4'-pyridylacetonitrile

hydrochloride salt (15.0 g, 97 mmol) and triethylbenzylammonium chloride (0.34 g, 1.49 mmol) and stir the mixture overnight. Partition the reaction mixture between EtOAc and water, then extract with EtOAc. Combine the organic extracts, wash with water and brine, dry over Na_2SO_4 and concentrate to a residue. Vacuum distill the residue collecting the product 4-phenyl-2-(4'-pyridyl)butyronitrile at 160-200°C (13.32 g, 62%), ms = 222 (M^+)

Step B Combine 4-phenyl-2-(4'-pyridyl)butyronitrile (0.61 g, 2.68 mmol), NaCl (3.13 g, 53.6 mmol) and $AlCl_3$ (14.29 g, 107.2 mmol) and heat to 180 °C. After 30 minutes, cool the reaction mixture to 0 °C and pour it into water. Add 15% NaOH (aqueous) until the solution is clear and basic. Extract with ether, combine the ethereal extracts, wash with water and brine, dry over Na_2SO_4, and concentrate to a residue. Chromatograph the residue on silica gel using 100% EtOAc to obtain 0.45 g (75%) of the title compound, mp 87-90°C

Preparation 7: trans-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthyl-1-amine

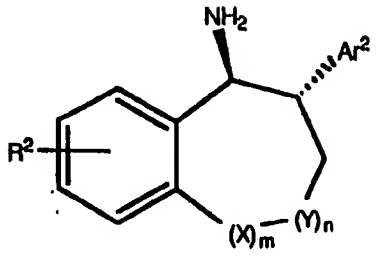
Step A Add DIBAL-H (83.8 mL, 83.8 mmol, 1 M in THF) dropwise to a -78 °C solution of 2-(4'-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-1-one (7.15 g, 27.94 mmol) in anhydrous THF (150 mL). Allow the reaction to come to room temperature overnight. Cool the mixture to 0 °C and quench with sodium sulfate decahydrate. Stir the mixture overnight, then vacuum filter and thoroughly wash the filtercake with THF. Concentrate the filtrate *in vacuo*, then chromatograph the resulting oil on silica gel using 20% EtOAc/hexanes to give a solid. Recrystallize from EtOAc/hexane to obtain 4.84 g (67%) of 2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol, mp 89-90.5°C.

Step B Add Ph_3P (4.54 g, 17.3 mmol) to a -20 °C (dry ice/carbon tetrachloride) solution of 2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (3.52 g, 13.84 mmol) in THF (100 mL). Add DEAD (3.05 mL, 19.4 mmol) dropwise to the mixture, followed by addition of diphenylphosphoryl azide (3.72 mL, 17.3 mmol) in the same

manner. Allow the mixture to warm to room temperature overnight. Concentrate the reaction mixture to a residue and chromatograph the residue on silica gel using 20% EtOAc/hexane to obtain 3.46 g of an oil containing the desired trans-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphtha-1-azide (TLC: R*f*=0.42 (20% EtOAc/hexane), yellow, Ce stain).

Dissolve the oil in EtOH (150 mL), purge with nitrogen and add 10% Pd/C (0.35 g). Hydrogenate the suspension on a Parr apparatus at 55 psi overnight. Filter the mixture through celite and thoroughly wash the filter cake with 25% MeOH/ CH_2Cl_2 (300 mL). Concentrate the filtrate *in vacuo* to a residue and chromatograph on silica gel using 5% MeOH/ CH_2Cl_2 to give 1.99 g of the title compound, ms = 254 (M+1).

Using a similar procedure, the following compounds can also be prepared:



Compound #	Ar^2	R^2	X	Y	m	n	physical data
7A	2-methoxy-phenyl	H	-	CH_2	0	1	ms = 254 (M^+1)
7B	3-methoxy-phenyl	H	-	-	0	0	ms = 239 (M^+)
7C	3-methoxy-phenyl	H	-	CH_2	0	1	ms = 254 (M^+1)
7D	C_6H_5	H	-	O	0	1	^{1}H NMR: δ 7.66 (1H, d, J= 7.6 Hz); 7.40 (3H, m); 7.32 (3H, m); 7.04 (1H, t, J= 7.3 Hz); 6.94 (1H, d, J= 8.6 Hz); 4.41 (1H, dd, J= 3.8, 11.2 Hz); 4.29 (2H, m); 3.05 (1H, dt, J= 9.6, 3.7 Hz); 2.21 (2H, br s).
7E	4-methoxy-phenyl	H	-	-	0	0	ms 239 (M^+)
7F	4-methoxy-phenyl	H	CH_2	CH_2	1	1	mp 82-82.5°C

Compound #	Ar^2	R^2	X	Y	m	n	physical data
7G	4-pyridyl	H	-	CH_2	0	1	mp 87-88°C
7H	C_6H_5	6-CH_3O-	-	-	0	0	^1H NMR: δ 7.38- 7.15 (m, 6H); 6.88- 6.77 (m, 2H); 4.32 (d, J= 9.7Hz, 1H); 3.79 (s, 3H); 3.24- 2.98 (m, 3H); 1.13 (br s, 2H)
7I	C_6H_5	7-CH_3O-	-	CH_2	0	1	mp 140-141°C
7J	C_6H_5	5-CH_3O-	-	CH_2	0	1	mp 130-131°C
7K	C_6H_5	6-CH_3O-	-	CH_2	0	1	IR (KBr) 3431, 3243, 1593, 1546 cm^{-1}
7L	4-methoxy-phenyl	7-CH_3O-	-	CH_2	0	1	mp 79-80°C

Preparation 8: cis-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthyl-1-amine

Step A Heat a mixture of 2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-one (6.22 g, 24.7 mmol), hydroxylamine hydrochloride (5.14 g, 74 mmol), NaOAc (6.1 g, 74 mmol), water (12 mL) and MeOH (45 mL) at reflux overnight. Concentrate the reaction mixture to approximately 50% of its original volume, dilute with water and cool to room temperature. Partition between EtOAc and water and extract the aqueous phase with EtOAc. Combine the organic extracts, wash with water and brine, dry over Na_2SO_4, and concentrate to a residue. Chromatograph the residue on silica gel using 15% EtOAc/hexane, then recrystallize from EtOAc/hexanes to obtain the desired oxime, mp 124-125°C.

Step B Add a solution of chlorodiphenylphosphine (3.98 mL, 22.2 mmol) in CH_2Cl_2 (20 mL), via cannula, to a -40 °C solution of the oxime from step A (5.93 g, 22.2 mmol) and Et_3N (3.1 mL, 22.2 mmol) in a 1:1 mixture of CH_2Cl_2/petroleum ether (50 mL each). Allow the reaction mixture to slowly warm to room temperature (~2h). Analyze the reaction mixture by TLC (50% EtOAc/hexane) to check for the presence of starting material. If starting material remains, re-cool the reaction mixture to -40 °C and treat with Et_3N (0.62 mL, 4.4 mmol) and chlorodiphenylphosphine (0.80 mL, 4.4 mmol). Again allow the mixture to warm to room temperature. Filter the solution and concentrate the filtrate *in vacuo* to a foam. Dissolve the foam in benzene, dry over Na_2SO_4, filter and concentrate *in vacuo* to isolate the phosphinylimine (11.48 g, ~115% crude yield).

Dissolve the phosphinylimine (10.32 g, 22.9 mmol) in dry THF (200 mL) and cool to -78 °C. Add DIBAL-H (68.6 mL, 68.6 mmol, 1M in THF) slowly via syringe. The reaction is complete in <10 min. Quench at -78 °C by the addition of solid sodium sulfate decahydrate and allow the mixture to warm slowly to room temperature. Filter the mixture and thoroughly wash the filter cake with THF. Concentrate the filtrate and recrystallize from benzene/hexane to give the phosphonamide, mp 204-204.5°C.

Step C Add 6N aqueous HCl (100 mL) to a room temperature solution of the phosphonamide from step B (8.68 g, 19.1 mmol) in MeOH (300 mL). Stir the mixture overnight, then concentrate the mixture *in vacuo* and partition the residue between 3N HCl and EtOAc. Extract with EtOAc, reserving the organic extracts. Adjust the pH of the aqueous layer to pH ~9 with aqueous Na_2CO_3 (saturated). Extract with CH_2Cl_2, combine the CH_2Cl_2 extracts, wash with water, dry over Na_2SO_4 and concentrate to give the title compound (2.73 g, 56%). Analyze the original EtOAc extracts by TLC to check for some of the desired amine. Combine these extracts, stir with aqueous Na_2CO_3 (saturated), wash successively with Na_2CO_3 (saturated), water and brine, then concentrate to a residue. Chromatograph the residue on silica gel with 50% EtOAc/hexane containing 1% Et_3N to obtain an additional 1.24 g of the desired amine. Total yield for the reaction is 3.97 g (82%) of the title compound, ms = 254 (M^+1).

The following compounds can be prepared using a similar procedure:
cis-2-phenyl-1,2,3,4-tetrahydronaphthyl-1-amine, ms = 224 (M^+1);
cis-6-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthyl-1-amine, mp 177-178°C;
cis-2-(3'-methoxyphenyl)-1,2,3,4-tetrahydronaphthyl-1-amine, ms = 254 (M^+1);
cis-5-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthyl-1-amine, ms = 254 (M^+1);
cis-7-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthyl-1-amine, mp 70-71°C;
cis-7-methoxy-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydro-naphthyl-1-amine, ms = 283 (M^+).

Preparation 9: cis-2-(4'-methoxyphenyl)benzosuberamine

Step A Slowly add $NaBH_4$ (1.84 g, 48.7 mmol) in small portions to a 0 °C solution of 2-(4'-methoxyphenyl)benzo-suberone (4.32 g, 16.2 mmol) in MeOH (75 mL). Allow the mixture to stir until gas

evolution ceases (~10 min). Quench by the addition of aqueous 3N HCl (10 mL). Remove most of the solvent *in vacuo*. Partition the residue between 3N HCl and EtOAc. Extract with EtOAc, then combine the extracts, wash with water and brine, dry over anhydrous Na_2SO_4 and concentrate to 3.7 g.of an oil.

Dissolve the oil in toluene (75 mL), add pTSA (0.31 g, 0.16 mmol) and heat the mixture at reflux overnight, removing the water as an azeotrope. Cool the mixture to room temperature, dilute with EtOAc, and extract with EtOAc. Combine the extracts, wash successively with aqueous Na_2CO_3 (sat.), water and brine, dry over Na_2SO_4 and concentrate to a residue. Crystallize from ether/ hexane to provide the desired olefin, mp 80-81°C.

Step B Add borane THF complex (27.6 mL, 27.6 mmol, 1M in THF) to a 0 °C solution of the olefin from step A (3.14 g, 12.5 mmol) in THF (50 mL). Allow the solution to warm to room temperature overnight. Cool the solution to 0 °C and add 3N aqueous NaOH (28 mL), then slowly add 30% H_2O_2 (28 mL). Stir the resulting mixture overnight, then extract with EtOAc. Combine the extracts, wash successively with aqueous $NaHCO_3$ (saturated), water and brine, dry over Na_2SO_4, filter and concentrate to a solid. Recrystallize the solid from EtOAc/hexane to afford the desired alcohol, mp 87.5-88.5°C.

In a manner similar to that in preparation 7, step B, the alcohol from step B is converted to the title compound, ms = 267 (M^+).

Using a similar procedure, cis-2-(2'-methoxyphenyl)-1,2,3,4-tetrahydronaphthylamine, ms = 254 (M^+1), can also be prepared.

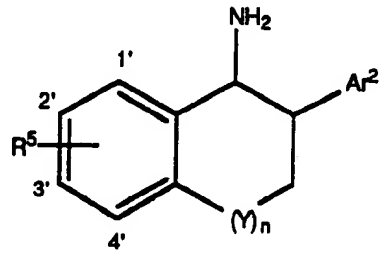
Preparation 10: 2-(4'-methoxyphenyl)indanamine

Step A Combine 2-(4'-methoxyphenyl)indanone (67.81 g, 285 mmol), methoxylamine hydrochloride (35.69 g, 427 mmol), NaOAc (35.04 g, 427 mmol), and MeOH (750 mL) under N_2. Stir the mixture at 60-65°C for 5 h, then overnight at room temperature. Pour the reaction mixture into two volumes of water and extract three times with 1:1 hexane/ EtOAc. Wash the combined extracts with water and brine, and

dry over Na_2SO_4. Filter the mixture and evaporate the solvent to obtain the oxime methyl ether (72.1 g, 100%).

Step B Treat the oxime methyl ether from step A (72.1 g, 285 mmol) with 1 M borane in THF (700 mL, 700 mmol) under N_2. Stir the mixture at room temperature overnight, then at reflux for 5 h. Cool the reaction mixture, and quench the excess borane with water. When bubbling ceases, bring the mixture to ca. pH 1 with concentrated HCl, stir vigorously at 50°C for 2 h, then stir at room temperature for 5 h more. Pour the mixture into water and extract twice with diethyl ether. Basify the aqueous phase to pH 9-10 with KOH and extract three times with ether. Combine the latter organic extracts , wash with brine and dry with Na_2SO_4. Filter the solution and evaporate the solvent to give the title compound as a mixture of cis and trans isomers (ca. 10:1). Filter the crude product through silica gel (EtOAc) to partially purify the title compound, ms = 239 (M^+).

Using a similar procedure, the following compounds can also be prepared:



Compound #	Ar^2	R^5	Y	n	physical data
10A	cis-3-methoxy-phenyl	H	-	0	ms = 239 (M^+)

Compound #	Ar^2	R^5	Y	n	physical data
10B	cis-3-nitro-phenyl	H	-	0	^{1}H NMR: δ 8.10 (m, 2H); 7.58-7.24 (m, 6H); 4.67 (d, J= 4.5Hz, 1H); 3.83 (dd, J= 8.0, 4.5Hz, 1H); 3.40-3.22 (m, 2H); 1.18 (br s, 2H)
10C	cis-4-nitro-phenyl	H	-	0	ms = 254 (M^+)
10D	cis-C_6H_5	3'-MeO	-	0	^{1}H NMR: δ 7.38-7.16 (m, 6H); 6.88-6.76 (m, 2H); 4.49 (d, J= 6.8Hz, 1H); 3.81 (s, 3H); 3.72 (app q, J= 7.2Hz, 1H); 3.21 (ddd, J= 15.4, 7.7, 7.2Hz, 2H); 1.14 (br s, 2H)
10E	cis-C_6H_5	H	O	1	
10F	trans-3-nitro-phenyl	H	-	0	^{1}H NMR: δ 8.29 (m, 1H); 7.74 (d, J= 6.3Hz, 1H); 7.57-7.24 (m, 6H); 4.42 (d, J= 6.5Hz, 1H); 3.31-3.05 (m, 3H); 1.19 (br s, 2H)
10F	trans-4-nitro-phenyl	H	-	0	ms = 254 (M^+)
10G	cis-C_6H_5	2'-MeO	-	0	^{1}H NMR: δ 7.30-7.00 (m, 6H); 6.85 (d, 1H, J=1Hz); 6.72 (dd, 1H, J=1.4Hz); 3.72 (s,3H); 3,62 (m, 1H); 3.10 (m, 2H).

Preparation 11: resolution of 2-(4'-methoxyphenyl)-indanamine

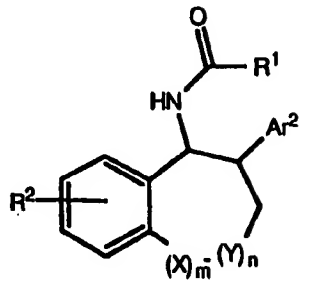
Dissolve the title amine (racemic), obtained from preparation 10, step B, in 2.5 L hot EtOH. Slowly add a hot solution of 100 g di-p-toluoyl-D-tartaric acid in EtOH (500 mL), and allow the solution to stand at room temperature overnight. Collect the crystals and wash with EtOH and 1:1 hexane:ether. Concentrate the filtrate under vacuum to ca. 500 mL then basify with NaOH. Extract with three 1 L portions of ether. Wash the combined ether layers with brine and dry over Na_2SO_4. Filter the solution, evaporate the solvent, dissolve the residue in 1 L of hot EtOH and treat with a hot solution of 55 g of di-p-toluoyl-L-tartaric acid in 700 mL EtOH. Allow the solution to stand overnight at room temperature and collect the crystals using the procedure described above to give 63 grams of a single enantiomer of the title compound.

The opposite enantiomer can be similarly prepared by using di-p-toluoyl-D-tartaric acid and di-p-toluoyl-L-tartaric acid in the reverse order.

Example 1: cis-N-[-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-α-phenylbenzeneacetamide

Add diphenylacetyl chloride (2.14 g, 9.28 mmol) to a 0 °C solution of cis-2-(p-methoxyphenyl)-1,2,3,4-tetrahydronaphthyl-1-amine (1.96 g, 7.74 mmol) and Et_3N (1.62 mL, 11.6 mmol) in CH_2Cl_2 (100 mL). Analyze the reaction mixture by TLC (5% MeOH/ CH_2Cl_2, Ce stain) to determine when consumption of the the starting amine is complete. Dilute the reaction mixture with water and CH_2Cl_2 and stir until all the solids dissolve. Wash with water, dry over Na_2SO_4 and concentrate *in vacuo* to a solid. Recrystallize from CH_2Cl_2/hexanes to give 2.92 g (84%) of the title compound, mp 215-215.5°C.

Using a similar procedure, the following compounds can also be prepared:



Compound #	Ar^2	R^2	O -CR¹	cis or trans	X	Y	m	n	physical data
1A	2-methoxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 215-216°C
1B	2-methoxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 216-217°C
1C	3-methoxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 138-139°C
1D	3-methoxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 213-214
1E	C_6H_5	H	2,2-diphenyl-acetyl	cis		O	0	1	mp 169.5-170°C
1F	4-methoxy-phenyl	H	2,2-dimethyl-undecan-oyl	trans	-	CH_2	0	1	mp 74-75°C

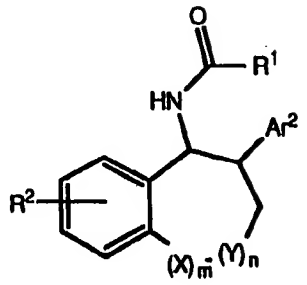
Compound #	Ar^2	R^2	$-\overset{O}{\overset{\|}{C}}R^1$	cis or trans	X	Y	m	n	physical data
1G	4-methoxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 251-252°C
1H	4-methoxy-phenyl	H	2,2-diphenyl-acetyl	cis	CH_2	CH_2	1	1	mp 155-156°C
1I	4-methoxy-phenyl	H	2,2-diphenyl-acetyl	trans	CH_2	CH_2	1	1	mp 235-235.5°C
1J	4-pyridyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 237.5-238°C
1K	C_6H_5	6-MeO-	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 188-189°C
1L	C_6H_5	6-MeO-	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 259-260°C
1M	C_6H_5	H	2,2-diphenyl-acetyl	trans	-	O	0	1	mp 217-219°C
1N	C_6H_5	7-MeO-	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 198-199°C
1O	C_6H_5	7-MeO-	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 266-268°C (dec.)
1P	C_6H_5	5-MeO-	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 217-218°C

Compound #	Ar^2	R^2	$-\overset{O}{\overset{\|}{C}}-CR^1$	cis or trans	X	Y	m	n	physical data
1Q	C_6H_5	5-MeO-	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 238-239°C
1R	4-methoxy-phenyl	7-MeO	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp = 258-259°C
1S	4-methoxy-phenyl	7-MeO	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp = 208-210°C (dec.)

Example 2: cis-N-[2-(4'-methoxyphenyl)indanyl]-α-phenylbenzeneacetamide

Dissolve 1.25 grams of cis-2-(4'-methoxyphenyl)-indanamine in CH_2Cl_2 (30 mL) and treat the solution sequentially with HOBT (607 mg, 4.494 mmol), diphenylacetic acid (1.143 g, 5.393 mmol), and EDCI (1.033 g, 5.393 mmol). Stir the mixture at room temperature for 1 h, then pour into water and extract twice with 1:1 hexane/ EtOAc. Wash the organic phase once with 1 N HCl (aq.), twice with aqueous K_2CO_3, and once with brine. Dry the organic solution with Na_2SO_4, then filter and evaporate the filtrate. Flush the resulting residue through a pad of silica gel (1:1 hexane/EtOAc) and evaporate to give a solid. Purify the solid by preparative, normal phase HPLC (4:1 hexane/EtOAc) to provide 1.077 g of the title compound, mp 168-170°C.

Using a similar procedure, the following compounds can also be prepared:



Compound #	Ar^2	R^2	O -CR¹	cis or trans	X	Y	m	n	physical data
2A	3-methoxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	-	0	0	mp 144-146°C
2B	3-methoxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	-	0	0	mp 169-171°C
2C	3-nitro-phenyl	H	2,2-diphenyl-acetyl	cis	-	-	0	0	mp 201-203°C
2D	3-nitro-phenyl	H	2,2-diphenyl-acetyl	trans	-	-	0	0	mp 185-187°C
2E	C_6H_5	7-MeO-	2,2-diphenyl-acetyl	cis	-	-	0	0	mp 211-212°C
2F	4-methoxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	-	0	0	197-199°C

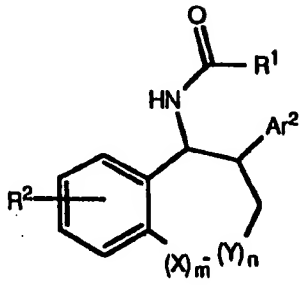
Compound #	Ar^2	R^2	$-\overset{O}{\overset{\|}{C}}R^1$	cis or trans	X	Y	m	n	physical data
2G	4-methoxy-phenyl	H	oleoyl	cis	-	CH_2	0	1	ms = 518 (M+1)
2H	4-methoxy-phenyl	H	oleoyl	trans	-	CH_2	0	1	ms 518 (M+1)
2I	4-nitro-phenyl	H	2,2-diphenyl-acetyl	cis	-	-	0	0	mp 218-219°C
2J	4-nitro-phenyl	H	2,2-diphenyl-acetyl	trans	-	-	0	0	mp 215-216°C
2K	C_6H_5	5-MeO-	2,2-diphenyl-acetyl	trans	-	-	0	0	mp 190-192°C
2L	C_6H_5	H	oleoyl	cis	-	CH_2	0	1	ms = 488 (M^+)
2M	C_6H_5	H	oleoyl	trans	-	CH_2	0	1	ms = 488 (M^+)
2N	C_6H_5	H	oleoyl	cis	-	O	0	1	mp 88-89°C
2O	C_6H_5	H	oleoyl	trans	-	O	0	1	ms = 490 (M^+)
2P	4-amino-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 229.5-230.5°C

Compound #	Ar^2	R^2	O -CR^1	cis or trans	X	Y	m	n	physical data
2Q	C_6H_5	6-MeO	2,2-diphenyl-acetyl	cis	-	-	0	0	mp = 160-162°C
2R	C_6H_5	5-MeO-	2,2-diphenyl-acetyl	cis	-	-	0	0	mp = 182-184°C
2S	C_6H_5	H	2,2-diphenyl-acetyl	cis	-	-	0	0	mp = 172-174°C
2T	C_6H_5	6-MeO-	2,2-diphenyl-acetyl	trans	-	-	0	0	mp = 205-207°C (dec.)

Example 3: cis-N-[2-(4'-hydroxyphenyl)indanyl]-α-phenylbenzeneacetamide

Dissolve cis-N-[2-(4'-methoxyphenyl)indanyl]-α-phenylbenzeneacetamide (27.80 g, 64.20 mmol) in CH_2Cl_2 (500 mL) in a flask under N_2. Add a solution of BBr_3 (1.0 M in CH_2Cl_2) via syringe until the reaction is complete as determined by TLC analysis. [A total of 160 mL (160 mmol) of the BBr_3 solution is required.] Pour the reaction mixture into water and extract three times with ether. Combine the ether extracts, wash once with water, twice with aqueous $Na_2S_2O_3$ solution, and once with brine, then dry over Na_2SO_4. Filter the ethereal solution and concentrate to a residue. (If the residue is highly colored, filter it through silica gel, eluting first with CH_2Cl_2, and then with CH_2Cl_2/ether to purify.) Dissolve the product in CH_2Cl_2, dilute with an equal volume of hexane, and heat the mixture to boiling until crystallization commences. Heat the mixture for an additional 10-15 min and then cool to room temperature. Collect the crystals by suction filtration, wash thoroughly with 5:1 hexane/ EtOAc, then with hexane, and air dry to provide the title compound (24.68 g, 91.7%), mp 165.5-167.5°C.

Using similar procedures, the following compounds can also be prepared:



Compound #	Ar^2	R^2	O -CR¹	cis or trans	X	Y	m	n	physical data
3A	2-hydroxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 258-259°C
3B	3-hydroxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	-	0	0	mp 178-180°C
3C	3-hydroxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 185-186°C
3D	3-hydroxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 207-208°C
3E	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	-	0	0	mp 188-190°C
3F	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 211.5-212°C

Compound #	Ar^2	R^2	$-C(=O)-CR^1$	cis or trans	X	Y	m	n	physical data
3G	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 204-206°C
3H	4-hydroxy-phenyl	H	2,2-dimethyl-undecanoyl	trans	-	CH_2	0	1	mp 148.5-149°C
3I	4-hydroxy-phenyl	H	$-C(=O)-CN(phenyl)_2$	trans	-	CH_2	0	1	mp 213.5-215°C
3J	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	trans	CH_2	CH_2	1	1	mp 184-185°C
3K	C_6H_5	5-OH	2,2-diphenyl-acetyl	cis	-	-	0	0	mp 171-172°C
3L	C_6H_5	5-OH	2,2-diphenyl-acetyl	trans	-	-	0	0	mp 209-211°C
3M	C_6H_5	6-OH	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 254-255°C
3N	C_6H_5	6-OH	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 248-250°C
3O	2-hydroxy-phenyl	H	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 267-268°C

Compound #	Ar^2	R^2	O :: - CR^1	cis or trans	X	Y	m	n	physical data
3P	C_6H_5	7-OH	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 177-178°C
3Q	C_6H_5	7-OH	2,2-diphenyl-acetyl	trans racemic	-	CH_2	0	1	mp 220-222°C (dec.)
3R	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	cis	CH_2	CH_2	1	1	196.5-197.5°C
3S	C_6H_5	5-OH	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp 219-220°C
3T	C_6H_5	5-OH	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp 210-211°C
3U	4-hydroxy-phenyl	7-OH	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp = 241-242°C
3V	4-hydroxy-phenyl	7-OH	2,2-diphenyl-acetyl	cis	-	CH_2	0	1	mp = 242-243°C
3W	C_6H_5	6-OH	2,2-diphenyl-acetyl	cis	-	-	0	0	mp = 195-197°C

Compound #	Ar^2	R^2	$-\overset{O}{\overset{\|}{C}}R^1$	cis or trans	X	Y	m	n	physical data
3X	C_6H_5	7-OH	2,2-diphenyl-acetyl	cis	-	-	0	0	mp = 146-147°C
3Y	C_6H_5	7-OH	2,2-diphenyl-acetyl	(+)-trans isomer	-	CH_2	0	1	mp = 220-222°C (dec.
3Z	C_6H_5	7-OH	2,2-diphenyl-acetyl	(-)-trans isomer	-	CH_2	0	1	mp = 220-222°C
3AA	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	(+)-cis isomer	-	-	0	0	mp = 165-167°C
3BB	4-hydroxy-phenyl	H	2,2-diphenyl-acetyl	(-)-cis isomer	-	-	0	0	mp = 164-165°C
3CC	C_6H_5	8-OH	2,2-diphenyl-acetyl	trans	-	CH_2	0	1	mp = 218-219°C

Example 6: trans-N'-[2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-N,N-diphenylurea

Add triphosgene (0.46 g, 1.55 mmol) to a room temperature solution of trans-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydronaphthyl-1-amine (1.19 g, 4.71 mmol) and Et_3N (0.72 mL, 5.18 mmol) in THF (20 mL). After 15 min, add diphenylamine (0.80 g, 4.71 mmol) and heat the mixture at reflux overnight. Cool to room temperature, dilute with water and EtOAc, and extract with EtOAc. Combine the extracts, wash with water and brine, dry over Na_2SO_4, and concentrate to a residue. Chromatograph the residue on silica gel with 20-60% EtOAc/hexane to provide the title compound 1.14 g (54%), mp 186.5-187.5°C.

Example 7: (+)-cis-N-[2-(3'-bromo-4'-hydroxyphenyl)indanyl]-α-phenylbenzeneacetamide

Add 0.262 g (1.472 mmol) of NBS to the compound of Example 3AA, (0.596 g, 1.422 mmol) in 10 mL of dry DMF at 0°C. Stir the mixture at 0°C for 30 min. then at room temperature for 4 hours. Pour the mixture into water and extract with EtOAc. Wash the EtOAc extract with water, then dry the extract over Na_2SO_4. Filter then evaporate the solvent to give a residue. Chromatograph the residue over silica gel (10:1 CH_2Cl_2/EtOAc) to give 0.479 g of the title compound, mp 158-159°C.

Example 8: cis-N-[2-(3'-chloro-4'-hydroxyphenyl)-indanyl]-α-phenylbenzeneacetamide

Dissolve the product of Example 3 (1.0 g) in 30 mL of dry CH_2Cl_2. Slowly add (dropwise) 0.09 mL of sulfuryl chloride followed by 3 mL of anhydrous ether. Stir the mixture at room temperature for 2 hours, then slowly pour the mixture into ice water. Extract with CH_2Cl_2, wash the extract with water, then dry the extract over $MgSO_4$. Filter, evaporate the solvent, then recrystallize the residue from CH_2Cl_2/hexane to give the title compound, mp 151-152°C.

Using substantially the same procedure, cis-N-[2-(3',5'-dichloro-4'-hydroxyphenyl)indanyl]-α-phenylbenzeneacetamide (8A), mp 118-120°C, can be prepared.

Example 9: (+)-cis-N-[2-(4'-hydroxy-3'-methylphenyl)indanyl]-α-phenylbenzeneacetamide

Combine the compound of Example 3AA (5.0 g) in 30 mL of 37% aqueous formaldehyde with 25 mL of 10 % KOH (aqueous) in 100 mL of DMF and heat the mixture at 65-70°C for 2 hours. Add 10 mL of formaldehyde and 10 mL of 10 % KOH and continue heating for 2 hours. Pour the mixture into water and extract with EtOAc. Treat the aqueous layer with brine and again extract with EtOAc. Combine the extracts and dry over Na_2SO_4, then filter and evaporate to a residue. Chromatograph the residue over silica gel (using 1:1 hexane/EtOAc) to give 0.45 g of monohydroxymethylated product and 0.48 g of bis-hydroxymethylated product.

Dissolve the monohydroxymethylated product (1.0 g) in 25 mL of HOAc containing 0.4 g of 20% $Pd(OH)_2$ on carbon. Hydrogenate under 60 PSI hydrogen for 24 hours. Chromatograph the product over silica gel (using 2:1 hexane/EtOAc) to give 0.313 g of the title compound, mp 150-151.5°C.

Hydrogenation using substantially the same procedure but starting with the bishydroxymethylated product gives (+)-cis-N-[2-(3',5'-dimethyl-4'-hydroxyphenyl)indanyl]-α-phenylbenzeneacetamide (9A), mp 162-164°C.

Using the assay methods described above, the compounds of Examples 1-9 were tested for in vitro ACAT inhibitory activity and for the ability to lower the level of cholesteryl esters in vivo. The results of these tests are as follows:

Example #	ACAT % Inhibition dose = 10 μM	% Reduction in cholesteryl esters (dose in mpk)
1	-13	0 (50)
1A	54.5	--
1B	53	21 (50)
1C	88.5	--
1D	75	0 (50)
1E	40	0 (50)
1F	36	0 (50)
1G	51	0 (50)
1H	84	0 (50)
1I	63	--
1J	94	-39 (50)
1K	43.6	--
1L	3	--
1M	85	0 (50)
1N	25	--
1O	28	--
1P	12	--
1Q	41	--
1R	65	0 (50)
1S	--	--
2	96	-17 (50)
2A	99	0 (50)
2B	94	--
2C	99	0 (50)
2D	90	--
2E	--	--
2F	19	0 (50)
2G	73	0 (100)
2H	81	0 (100)

Example #	ACAT % Inhibition dose = 10 μM	% Reduction in cholesteryl esters (dose in mpk)
2I	51	--
2J	-12	--
2K	90	17 (25)
2L	66	--
2M	99	0 (100)
2N	85	0 (100)
2O	87	--
2P	97	-57 (50) -46 (50) -15 (25)
2Q	16	--
2R	75	0 (50)
2S	83	16 (50)
2T	15	--
3	99	-89 (50) -87.5 (25) -71 (10)
3A	83	0 (50)
3B	97	0 (50)
3C	77	0 (50)
3D	98	0 (50)
3E	99	-52 (50)
3F	91	-16 (50)
3G	93	-57 (50) -43 (25)
3H	86	0 (50)
3I	99	-16 (50)
3J	96	-61 (50)
3K	54	0 (50)
3L	93	--

Example #	ACAT % Inhibition dose = 10 µM	% Reduction in cholesteryl esters (dose in mpk)
3M	87	-45 (50)
3N	92	0 (50)
3O	75	--
2P	75	0 (50)
3Q	94	-78 (50)
3R	75	0 (50)
3S	61	0 (50)
3T	80	0 (50)
3U	98	-97 (50) -86 (30) -60 (10)
3V	88	0 (50)
3W	84	14 (50)
3X	97	--
3Y	83	--
3Z	92	--
3AA	--	-88 (5) -73 (1) -56 (1)
3BB	<0	0 (5) 0 (1)
3CC	68	-20 (50)
4	94	0 (50)
4A	81	0 (50)
5	94	--
5A	95	0 (10)
6	97	-16 (50)
7	100	-40 (50)
8	99	-40 (50)
8A	99	-14 (50)
9	98	-66 (50)
9A	97	-60 (50)

The following formulations exemplify some of the dosage forms of this invention. In each the term "active compound" designates a compound of formula I, preferably N-[2-(4'-hydroxyphenyl)indanyl]-α-phenylbenzeneacetamide. However, this compound may be replaced by an equally effective amount of other compounds of formula I.

EXAMPLE A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B
Capsules

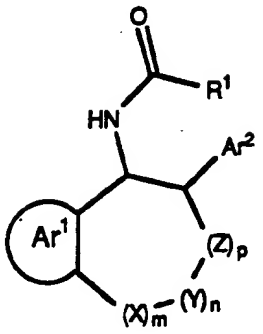
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

We claim:

1. A compound of the formula



wherein Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl or R^2-substituted heteroaryl, wherein R^2 is 1 to 3 substituents independently selected from the group consisting of halogeno, hydroxy, lower alkyl, lower alkoxy, nitro, amino, lower alkylamino and lower dialkylamino;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(alkyl)-, $-C(alkyl)_2-$, -NH-, -N(alkyl)-, -O- and $-SO_r-$, wherein r is 0, 1 or 2, and m, n and p are 0 or 1, such that $0< (m+n+p) <4$, provided that only one of X,Y or Z is -NH-, -N(alkyl)-, -O- and $-SO_r-$;

R^1 is an alkyl chain of 1 to 25 carbon atoms, branched or straight, saturated or containing one or more double bonds; an alkyl chain of 1 to 25 carbon atoms as defined substituted by one or more substituents selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl and R^2-substituted heteroaryl; an alkyl chain of 1 to 25 carbon atoms as defined interrupted by one or more Q groups, wherein Q is independently selected from the group consisting of -O-, $-SO_r-$, phenylene, R^2-substituted phenylene, heteroarylene and R^2-substituted heteroarylene; an interrupted alkyl chain of 1 to 25 carbon atoms as defined substituted by one or more substituents selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl and R^2-substituted heteroaryl; an alkyl chain of 4 to 25 carbon atoms,

interrupted by one or more groups selected from the group consisting of Q, -NH-, -C(O)- and -N(lower alkyl)-; an interrupted alkyl chain of 4 to 25 carbon atoms as defined substituted by one or more substituents selected from the group consisting of phenyl, R^2-substituted phenyl, heteroaryl and R^2-substituted heteroaryl; a diphenylamino group; a di-(R^2-substituted phenyl)amino group; a diheteroarylamino group; or a di-(R^2-substituted heteroaryl)amino group;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a 6-C ring.

3. A compound of claim 1 wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a six membered ring containing one oxygen atom.

4. A compound of claim 1 wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a 7-C ring.

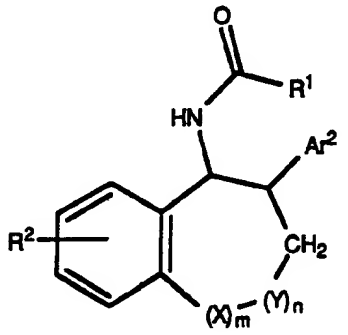
5. A compound of claim 1 wherein $-(X)_m-(Y)_n-(Z)_p-$, together with the carbons to which they are attached, form a 5-C ring.

6. A compound of claims 1, 2, 3, 4 or 5 wherein Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, nitro-substituted phenyl, amino-substituted phenyl, lower alkoxy-substituted phenyl, hydroxy-substituted phenyl and pyridyl.

7. A compound of claims 1, 2, 3, 4, 5 or 6 wherein $-C(O)-R^1-$ is selected from the group consisting of oleoyl, stearoyl, palmitoyl, linoleoyl, linolenoyl, elaidoyl, arachidonoyl, eicosapentaenoyl, eicosatetraenoyl, phenylacetyl, diphenylacetyl, 3,3-diphenylpropionyl, 2,2-dimethylundecanoyl, 2,3-diphenylpropionyl, 3-methoxy-4-(tetradecyloxy)benzoyl, 11-[N-(2,2-diphenylacetyl)amino]-undecanoyl, phenoxyundecanoyl and N,N-diphenylaminocarbonyl.

8. A compound of claims 1, 2, 3, 4, 5, 6 or 7 wherein -C(O)-R^1- is diphenylacetyl, 2,2-dimethylundecanoyl, oleoyl or N,N-diphenylaminocarbonyl.

9. A compound of claim 1 represented by the formula:



wherein

Compound #	cis or trans	R^2	Ar^2	O ‖ -CR^1	X	Y	m	n
1A	cis	H	2-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1B	trans	H	2-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1C	cis	H	3-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1D	trans	H	3-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1E	cis	H	C_6H_5	diphenyl-acetyl	-	O	0	1
1	cis	H	4-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1F	trans	H	4-methoxy-phenyl	2,2-dimethyl-undecanoyl	-	CH_2	0	1

Compound #	cis or trans	R^2	Ar^2	$-C(=O)R^1$	X	Y	m	n
1G	trans	H	4-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1H	cis	H	4-methoxy-phenyl	diphenyl-acetyl	CH_2	CH_2	1	1
1I	trans	H	4-methoxy-phenyl	diphenyl-acetyl	CH_2	CH_2	1	1
1J	trans	H	pyridyl	diphenyl-acetyl	-	CH_2	0	1
1K	cis	6-MeO-	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
1L	trans	6-MeO-	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
1M	trans	H	C_6H_5	diphenyl-acetyl	-	O	0	1
1N	cis	7-MeO-	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
1O	trans	7-MeO-	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
1P	cis	5-MeO-	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
1Q	trans	5-MeO-	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
1R	trans	7-MeO-	4-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
1S	cis	7-MeO-	4-methoxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
2A	cis	H	3-methoxy-phenyl	diphenyl-acetyl	-	-	0	0
2B	trans	H	3-methoxy-phenyl	diphenyl-acetyl	-	-	0	0

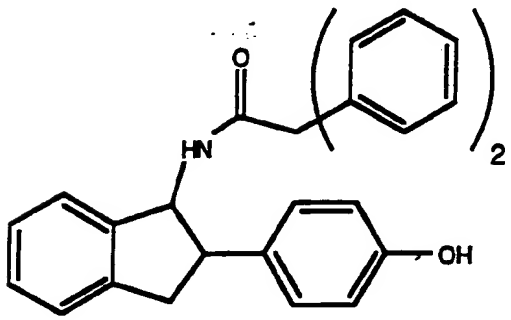
Compound #	cis or trans	R^2	Ar^2	$-C(=O)-R^1$	X	Y	m	n
2C	cis	H	3-nitro-phenyl	diphenyl-acetyl	-	-	0	0
2D	trans	H	3-nitro-phenyl	diphenyl-acetyl	-	-	0	0
2E	cis	7-OH	C_6H_5	diphenyl-acetyl	-	-	0	0
2F	trans	H	4-methoxy-phenyl	diphenyl-acetyl	-	-	0	0
2G	cis	H	4-methoxy-phenyl	oleoyl	-	CH_2	0	1
2H	trans	H	4-methoxy-phenyl	oleoyl	-	CH_2	0	1
2I	cis	H	4-nitro-phenyl	diphenyl-acetyl	-	-	0	0
2J	trans	H	4-nitro-phenyl	diphenyl-acetyl	-	-	0	0
2	cis	H	4-methoxy-phenyl	diphenyl-acetyl	-	-	0	0
2K	trans	5-MeO-	C_6H_5	diphenyl-acetyl	-	-	0	0
2L	cis	H	C_6H_5	oleoyl	-	CH_2	0	1
2M	trans	H	C_6H_5	oleoyl	-	CH_2	0	1
2N	cis	H	C_6H_5	oleoyl	-	O	0	1
2O	trans	H	C_6H_5	oleoyl	-	O	0	1
2P	trans	H	4-amino-phenyl	diphenyl-acetyl	-	CH_2	0	1
2Q	cis	6-MeO-	C_6H_5	diphenyl-acetyl	-	-	0	0
2R	cis	5-MeO-	C_6H_5	diphenyl-acetyl	-	-	0	0

Compound #	cis or trans	R^2	Ar^2	$-\overset{O}{\overset{\|}{C}}R^1$	X	Y	m	n
3A	trans	H	2-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3B	cis	H	3-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
3C	cis	H	3-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3D	trans	H	3-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3	cis	H	4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
3E	trans	H	4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
3F	cis	H	4-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3G	trans	H	4-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3H	trans	H	4-hydroxy-phenyl	2,2-dimethyl-undecanoyl	-	CH_2	0	1
3I	trans	H	4-hydroxy-phenyl	$-\overset{O}{\overset{\|}{C}}N(Ph)_2$	-	CH_2	0	1
3J	trans	H	4-hydroxy-phenyl	diphenyl-acetyl	CH_2	CH_2	1	1
3K	cis	5-OH	C_6H_5	diphenyl-acetyl	-	-	0	0
3L	trans	5-OH	C_6H_5	diphenyl-acetyl	-	-	0	0
3M	cis	6-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3N	trans	6-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1

Compound #	cis or trans	R^2	Ar^2	$-C(=O)-R^1$	X	Y	m	n
3O	cis	H	2-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3P	cis	7-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3Q	trans	7-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3R	cis	H	4-hydroxy-phenyl	diphenyl-acetyl	CH_2	CH_2	1	1
3S	trans	5-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3T	cis	5-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3U	trans	7-OH	4-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3V	cis	7-OH	4-hydroxy-phenyl	diphenyl-acetyl	-	CH_2	0	1
3W	cis	6-OH	C_6H_5	diphenyl-acetyl	-	-	0	0
3X	cis	7-OH	C_6H_5	diphenyl-acetyl	-	-	0	0
3Y	(+)-trans	7-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3Z	(-)-trans	7-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1
3AA	(+)-cis	H	4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
3BB	(-)-cis	H	4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
3CC	trans	8-OH	C_6H_5	diphenyl-acetyl	-	CH_2	0	1

Compound #	cis or trans	R^2	Ar^2	$-\overset{O}{\overset{\|}{C}}R^1$	X	Y	m	n
4A	cis	H	4-hydroxy-phenyl	oleoyl	-	CH_2	0	1
4	trans	H	4-hydroxy-phenyl	oleoyl	-	CH_2	0	1
5A	cis	H	3-amino-phenyl	diphenyl-acetyl	-	-	0	0
5	trans	H	4-amino-phenyl	diphenyl-acetyl	-	-	0	0
6	trans	H	4-methoxy-phenyl	$-\overset{O}{\overset{\|}{C}}N(Ph)_2$	-	CH_2	0	1
7	(+)-cis	H	3-bromo-4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
8	cis	H	3-chloro-4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
8A	cis	H	3,5-di-chloro-4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0
9	(+)-cis	H	4-hydroxy-3-methyl-phenyl	diphenyl-acetyl	-	-	0	0
9A	(+)-cis	H	3,5-di-methyl-4-hydroxy-phenyl	diphenyl-acetyl	-	-	0	0

10. A compound of claim 1 having the chemical structure



11. A pharmaceutical composition for treating atherosclerosis comprising an ACAT-inhibitory effective amount of a compound of claim 1 in a pharmaceutically effective carrier.

12. A pharmaceutical composition according to claim 11, said composition being in dosage form.

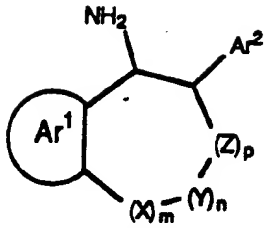
13. A method of treating atherosclerosis comprising administering to a mammal in need of such treatment a pharmaceutical composition of claim 11.

14. A method for preparing a pharmaceutical composition comprising admixing a compound of claim 1 with a pharmaceutically acceptable carrier.

15. The use of a compound of claim 1 for the manufacture of a medicament for treating atherosclerosis.

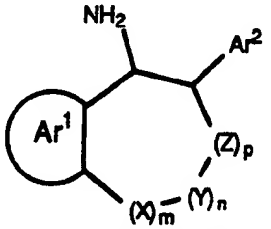
16. A process for the preparation of a compound of claim 1 comprising:

(a) reacting a carboxylic acid of the formula R^1-COCl, wherein R^1 is as defined in claim 1, with an amine of the formula



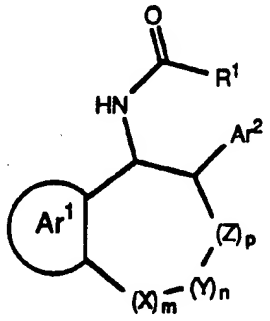
wherein Ar^1, Ar^2, X, Y, Z, m, n and p are as defined in claim 1, in the presence of tertiary amine base in a suitable solvent; or

(b) reacting a carboxylic acid of the formula R^1-COOH, as defined above, with an amine of the formula



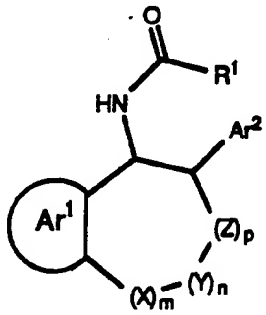
as defined above, in the presence of a coupling agent and a tertiary amine base in a suitable solvent; or

(c) for preparing a compound of claim 1, wherein one of Ar^1 or Ar^2 is R^2-substituted phenyl, wherein R^2 is hydroxy, reacting a compound of the formula



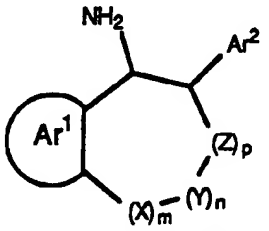
wherein R^1, X, Y, Z, m, n and p are as defined above, and one of Ar^1 or Ar^2 is R^2-substituted phenyl, wherein R^2 is methoxy, with BBr_3, or with a mixture of NaH and EtSH in DMF at reflux temperature; or

(d) for preparing a compound of claim 1, wherein one of Ar^1 or Ar^2 is R^2-substituted phenyl, wherein R^2 is a primary amino group, hydrogenating a compound of the formula



wherein R^1, X, Y, Z, m, n and p are as defined above, and one of Ar^1 or Ar^2 is R^2-substituted phenyl, wherein R^2 is a nitro group, in the presence of 5% Pd/C; or

(e) for preparing a compound of claim 1, wherein R^1 is N,N-diphenylamino, reacting an amine of the formula



as defined above, with triphosgene and Et_3N, then with diphenylamine at reflux temperature; or

(f) for preparing a compound of claim 1, wherein Ar^2 is 3-R^{2a}-5-R^{2b}-4-hydroxyphenyl, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, bromo, chloro and methyl, reacting a compound of claim 1, wherein Ar^2 is 4-hydroxyphenyl, with NBS, or sulfuryl chloride, or with formaldehyde and potassium hydroxide followed by hydrogen in the presence of 20% $Pd(OH)_2$;

followed by isolation of the preferred isomer , if desired, and removal of protecting groups, if necessary, to yield the desired product and if desired, preparation of a salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/02662

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C233/23; C07C233/14; C07C233/41; C07C275/32
C07D311/68; C07D213/40; C07C231/02; A61K31/165

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	JOURNAL OF THE CHEMICAL SOCIETY. 1957, LETCHWORTH GB pages 4760 - 4765; K. W. GOPINATH ET AL.: 'synthesis of some 1:2 -benzophenanthridines.' see page 4761 - page 4763 ---	1,2,6
X	COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES vol. 258, no. 6, 10 February 1964, MONTREUIL FR pages 1820 - 1823; COLETTE BROQUET ET AL.: 'Sur l'amino-1 phényl-2 tétrahydro-1.2.3.4 naphtalène.' see page 1821 --- -/--	1,2,6

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09 JULY 1992	13. 08. 92

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	RUFET J.

III. DOCUMENTS CONSIDERED TO . RELEVANT (CONTINUED FROM THE SECOND SHEE

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL AND PHARMACEUTICAL BULLETIN. vol. 19, no. 6, June 1971, TOKYO JP pages 1150 - 1157; TETSUJI KAMETANI ET AL.: 'phenolic cyclization. IX. Syntheses of Benz[c]phenanthridine and related Compounds' see page 1156	1,2,6
X	BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN. vol. 41, no. 9, September 1968, TOKYO JP pages 2073 - 2077; SHOZO YAMAGUCHI ET AL.: 'Syntheses of trans-Isoflavan-4-ols' see page 2076	1,3,6
X	CHEMICAL AND PHARMACEUTICAL BULLETIN. vol. 31, no. 9, September 1983, TOKYO JP pages 3056 - 3073; HISASHI ISHII ET AL.: 'Studies on the Chemical Constituents of Rutaceous Plants.' see page 3065 - page 3069	1,2,6
X	CHEMICAL ABSTRACTS, vol. 59, no. 1, 8 July 1963, Columbus, Ohio, US; TORIZO TAKAHASHI ET AL.: 'Syntheses of analgesics. XXX. Indanamine derivatives.' page 611 ; & Yakugaku Zasshi Vol. 82 , 1962 , pages 1597-1603 see abstract	1,5,6
X	EP,A,0 173 331 (OTSUKA PHARMACEUTICAL CO., LTD.) 5 March 1986 see abstract; claims 1,23	1,5
A	US,A,4 456 619 (FAIZULLA G. KATHAWALA) 26 June 1984 cited in the application see column 10, line 53 - column 12, line 58; claims 1,4,22-26	1,11-15
A	US,A,4 248 893 (FAIZULLA G. KATHAWALA) 3 February 1981 cited in the application see column 6, line 18 - column 9, line 10; claims 1,4,29	1,11-15

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9202662 SA 59871

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/07/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0173331	05-03-86	JP-A- 61069747	10-04-86
		DE-A- 3583780	19-09-91
		JP-A- 62129258	11-06-87
		US-A- 4895847	23-01-90
		US-A- 5055474	08-10-91
		US-A- 4788130	29-11-88
US-A-4456619	26-06-84	BE-A- 878812	17-03-80
		DE-A- 2937175	27-03-80
		FR-A- 2436133	11-04-80
		GB-A- 2030143	02-04-80
		JP-A- 55040695	22-03-80
US-A-4248893	03-02-81	US-A- 4185118	22-01-80
		US-A- 4201785	06-05-80
		US-A- 4384124	17-05-83

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 281/10 — A1

(11) International Publication Number: WO 93/16055

(43) International Publication Date: 19 August 1993 (19.08.93)

(21) International Application Number: PCT/GB93/00328

(22) International Filing Date: 16 February 1993 (16.02.93)

(30) Priority data:
9203347.1 17 February 1992 (17.02.92) GB

(71) Applicant *(for all designated States except US)*: THE WELLCOME FOUNDATION LIMITED [GB/GB]; Unicorn House, 160 Euston Road, London NW1 2BP (GB).

(72) Inventor; and

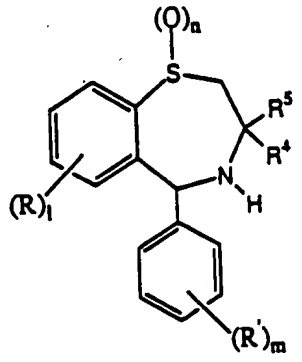
(75) Inventor/Applicant *(for US only)* : BRIEADDY, Lawrence, Edward [US/US]; 5924 Wintergreen Drive, Raleigh, NC 27609 (US).

(74) Agent: GARRETT, Michael; The Wellcome Foundation Limited, Langley Court, Beckenham, Kent BR3 3BS (GB).

(81) Designated States: AU, BR, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: HYPOLIPIDAEMIC BENZOTHIAZEPINE COMPOUNDS



(I)

(57) Abstract

The present invention is concerned with compounds of formula (I) wherein l is an integer of from 0 to 4; m is an integer of from 0 to 5; n is an integer of from 0 to 2; R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alk xy and alkyl groups are opti nally substituted by one or more halogen atoms; R^4 is a C_{1-6} straight alkyl group; and R^5 is a C_{2-6} straight alkyl group; and their salts, solvates and physiologically functional derivatives, with processes and novel intermediates for their preparation, with pharma-

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam

Hypolipidaemic benzothiazepine compounds

The present invention is concerned with new hypolipidaemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidaemic conditions, such as atherosclerosis.

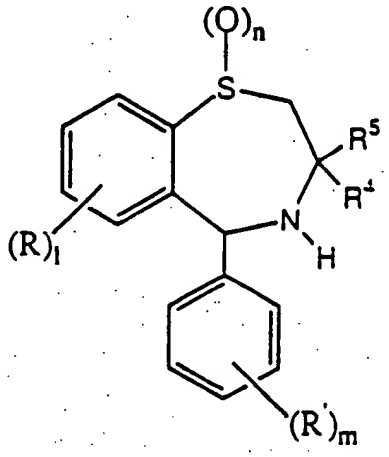
Hypolipidaemic conditions are often associated with elevated plasma concentrations of low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol. Such concentrations may be reduced by decreasing the absorption of bile acids from the intestine. One method by which this may be achieved is to inhibit the bile acid active uptake system in the terminal ileum. Such inhibition stimulates the conversion of cholesterol to bile acid by the liver and the resulting increase in demand for cholesterol produces a corresponding increase in the rate of clearance of LDL and VLDL cholesterol from the blood plasma or serum.

There has now been identified a novel class of heterocyclic compounds which reduce the plasma or serum concentrations of LDL and VLDL cholesterol and in consequence are particularly useful as hypolipidaemic agents. By decreasing the concentrations of cholesterol and cholesterol ester in the plasma, the compounds of the present invention retard the build-up of atherosclerotic lesions and reduce the incidence of coronary heart disease-related events. The latter are defined as cardiac events associated with increased concentrations of cholesterol and cholesterol ester in the plasma or serum.

For the purposes of this specification, a hyperlipidaemic condition is defined as any condition wherein the total cholesterol concentration (LDL + VLDL) in the plasma or serum is greater than 240mg/dL (6.21mm l/L) (J. Amer. Med. Assn. 256, 20. 2849-2858 (1986)).

USP 3,362,962 describes a genus of benz thiazepines outside the scope of the present invention which have muscle-relaxant and anticonvulsant activity; there is no disclosure in the patent specification that the compounds described therein may be useful as hypolipidaemic agents.

According to the present invention, there is provided a compound of formula (I)



(I)

wherein

l is an integer of from 0 to 4;

m is an integer of from 0 to 5;

n is an integer of from 0 to 2;

R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R" is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^4 is a C_{1-6} straight, that is, unbranched, alkyl group: and

R^5 is a C_{2-6} straight, that is, unbranched, alkyl group:

and salts, solvates and physiologically functional derivatives thereof.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, ie basic, compounds. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulphonic and sulphuric acids, and organic acids, such as acetic, benzenesulphonic, benzoic, citric, ethanesulphonic, fumaric, gluconic, glycollic, isothionic, lactic, lactobionic, maleic, malic, methanesulphonic, succinic, p-toluenesulphonic, tartaric and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

Salts having a non-pharmaceutically acceptable anion are within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in non-therapeutic, for example, in vitro, applications.

The term "physiologically functional derivative" as used herein refers to any physiologically acceptable derivative of a compound of the present invention, for example, an ester, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof.

A further aspect of the present invention is prodrugs of the compounds of the invention. Such prodrugs can be metabolised in vivo to give a compound according to the invention. These prodrugs may or may not be active in their own right.

The compounds of the present invention can also exist in different polymorphic forms, for example, amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds of the present invention are within the scope of the invention and are a further aspect thereof.

The term "alkyl" as used herein refers, unless otherwise stated, to a monovalent straight or branched chain radical. Likewise, the term "alkoxy" refers to a monovalent straight or branched chain radical attached to the parent molecular moiety through an oxygen atom. The term "phenylalkoxy" refers to a monovalent phenyl group attached to a divalent C_{1-6} alkylene group which is itself attached to the parent molecular moiety through an oxygen atom.

The compounds of formula (I) may exist in forms wherein one or both of the carbon centres $-C(R^4)(R^5)-$ and $-CHPh(R')_m-$ (wherein Ph is the phenyl group) is/are chiral. The present invention includes within its scope each possible optical isomer substantially free, ie associated with less than 5%, of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures.

For the purposes of this specification, the absolute chiralities of the aforementioned carbon centres are given in the order $-C(R^4)(R^5)-$, then $-CHPh(R')_m-$. For example, the prefix "(RS)-" denotes an (R)-configuration at $-C(R^4)(R^5)-$ and an (S)-configuration at $-CHPh(R')_m-$ and the prefix "(RS,SR)-" denotes a mixture of two isomers wherein one is (R)- at $-C(R^4)(R^5)-$ and (S)- at $-CHPh(R')_m-$ and the other is (S)- at $-C(R^4)(R^5)-$ and (R)- at $-CHPh(R')_m-$. Other permutations will be clear to the skilled person.

In those cases where the absolute stereochemistry at $-C(R^4)(R^5)-$ and $-CHPh(R')_m-$ has not been determined, the compounds of the invention are defined in terms of the relative positions of the R^4/R^5 and $H/Ph(R')_m$ substituents. Thus those compounds wherein the bulkier

of the R^4 and R^5 substituents, ie the substituent of higher mass, and the $Ph(R')_m$ substituent are both located on the same side of the thiazepine ring are referred to herein as "cis", and those compounds in which they are located on opposite sides of the ring are referred to as "trans". It will be evident to a skilled person that both "cis" and "trans" compounds of the invention can each exist in tw enantiomeric forms which are individually designated "(+)-" or "(-)-" according to the direction of rotation of a plane of polarised light when passed through a sample of the compound. Cis or trans compounds of the invention in which the individual enantiomers have not b en resolved are referred to herein using the prefix "(+-)-".

Preferred compounds of formula (I) having particularly desirable hypolipidaemic properties include those wherein

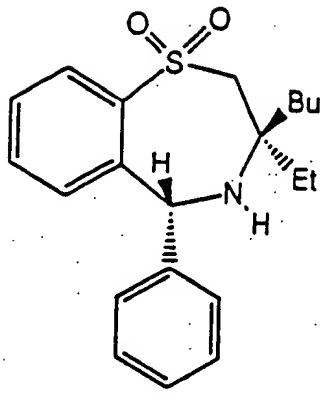
n is 2;

R^4 is methyl, ethyl, n-propyl, or n-butyl; and/or

R^5 is ethyl, n-propyl, or n-butyl.

Of these, the (RR)-, (SS)- and (RR,SS)-trans compounds are particularly preferred.

A compound of formula (I) having exceptional hypolipidaemic properties is trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide in both its (RR)- and (RR,SS)-forms, viz (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide and (+-)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide respectively. The former is especially preferred and is depicted thus:



According to further aspects of the invention, there are also provided:

(a) compounds of formula (I) and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof for use as therapeutic agents, particularly in the prophylaxis and treatment of clinical conditions for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis;

(b) pharmaceutical compositions comprising a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, or physiologically functional derivatives, at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents;

(c) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis;

(d) a method of inhibiting the absorption of bile acids from the intestine of a mammal, such as a human, which comprises

administering an effective bile acid absorption inhibiting amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;

(e) a method of reducing the blood plasma or serum concentrations f LDL and VLDL cholesterol in a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative there f to the mammal;

(f) a method of reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol and cholesterol ester reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;

(g) a method of increasing the faecal excretion of bile acids in a mammal, such as a human, which comprises administering an effective bile acid faecal excretion increasing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;

(h) a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis, which comprises administering a therapeutically effective amount of a compound of the formula (I) or of a pharmaceutically acceptable salt. solvate. r physiologically functional derivative thereof to the mammal:

(i) a method of reducing the incidence of coronary heart disease-related events in a mammal, such as a human, which comprises administering an effective coronary heart disease-related events reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof;

(j) a method of reducing the concentration of cholesterol in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I);

(k) processes for the preparation of compounds of formula (I) (including salts, solvates and physiologically functional derivatives thereof as defined herein); and

(l) compounds of formula (II) for use as intermediates in the preparation of compounds of formula (I).

Hereinafter all references to "compound(s) of formula (I)" refer to compound(s) of formula (I) as described above together with their salts, solvates and physiologically functional derivatives as defined herein.

The amount of a compound of formula (I) which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode of administration and the clinical condition of the recipient. In general, a daily dose is in the range of from 0.3mg to 100mg (typically from 3mg to 50mg) per day per kilogram bodyweight, for example, 3-10mg/kg/day. An intravenous dose can, for example, be in the range of from 0.3mg to 1.0mg/kg, which can conveniently be administered as an infusion of from 10ng to 100ng per kilogram per minute. Infusion fluids suitable for this purpose can

contain, for example, from 0.1ng to 10mg, typically fr m 1ng to 10mg, per millilitre. Unit doses can contain, for example, from 1mg to 10g of the active compound. Thus ampoules for injection can contain, f r example, from 1mg to 100mg and orally administrable unit d se formulations, such as tablets or capsules, may contain, for example, from 1.0 to 1000mg, typically from 10 to 600mg. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiazepine ion derived from the salt.

For the prophylaxis or treatment of the conditions referred to above, the compounds of formula (I) can be used as the compound per se, but are preferably presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present including other compounds of formula (I). The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound of formula (I) which is being used. Enteric-coated and enteric-coated contr lled release formulations are also within the scope of the invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and

anionic polymers of methacrylic acid and methacrylic acid methyl ester.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or moulding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets can be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I), preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration can also be effected by means

of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the inventi n will generally contain from 0.1 to 5% w/w of the active compound.

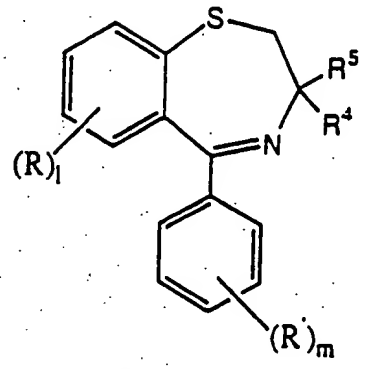
Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of formula (I) with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for exampl , from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be present d as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

The comp unds of the invention can be prepared by conventional meth ds known to a skilled person or in an anal gous manner t processes described in the art.

For example, compounds of formula (I) wherein n = 0 can be prepared by reducing the imine bond of a compound of formula (II)

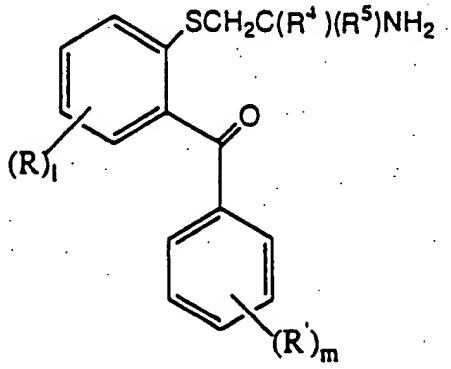


(II)

wherein l, m, R, R', R^4 and R^5 are as hereinbefore defined, using, for example, a boron compound, such as borane, in a suitable solvent, such as THF, or catalytic hydrogenation using, for example, a palladium catalyst, such as 10% Pd/C.

Compounds of formula (II) as herein defined are considered to be novel and constitute a further aspect of the present invention.

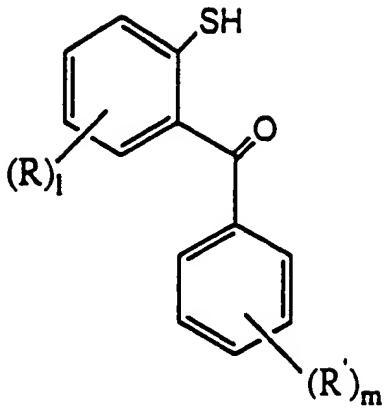
Compounds of formula (II) can be prepared by cyclising compounds of formula (III)



(III)

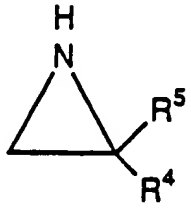
wherein l, m, R, R', R^4 and R^5 are as hereinbefore defined, by, for example, azeotropic distillation or refluxing in the presence of a suitable drying agent, such as molecular sieves, in a suitable solvent, for example, 2,6-lutidine, in the presence of an acid, such as HCl.

Compounds of formula (III) can be prepared by reacting a compound of formula (IV)



(IV)

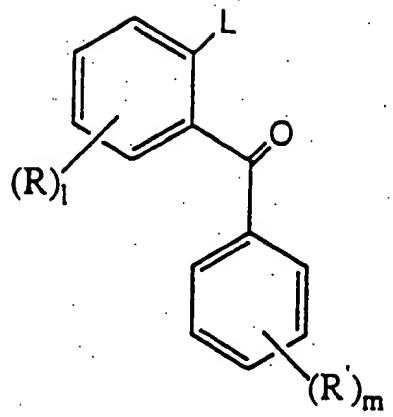
wherein l, m, R and R' are as hereinbefore defined, with a compound of formula (V)



(V)

wherein R^4 and R^5 are as hereinbefore defined, typically in a polar solvent, for example, methanol.

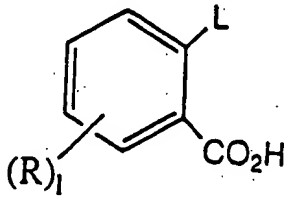
Compounds of formula (III) can also be prepared by reacting a compound of formula (XVIII)



(XVIII)

wherein l, m, R and R′ are as hereinbefore defined and L is a suitable leaving group, for example, halogen, with a compound of formula $HSCH_2C(R^4)(R^5)NH_2$ wherein R^4 and R^5 are as hereinbefore defined.

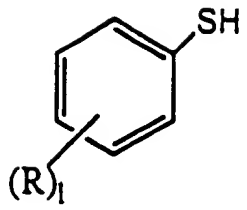
Compounds of formula (XVIII) can be prepared by reacting a compound of formula (XIX)



(XIX)

wherein l, L and R are as hereinbefore defined, with a compound of formula $Ph(R')_mH$ wherein Ph is a phenyl group and m and R′ are as hereinbefore defined, typically by a Friedel-Crafts reaction using, for example, aluminium chloride.

Compounds of formula (IV) can be prepared by reacting a compound of formula (VI)



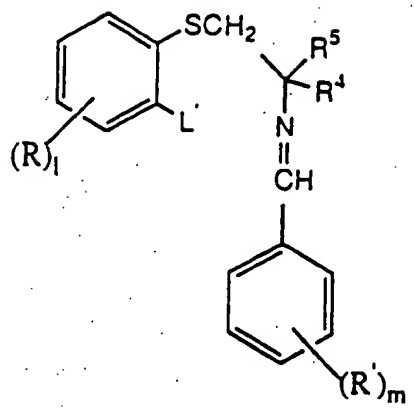
(VI)

wherein l and R are as hereinbefore defined, with a compound of formula $(R')_mPhCN$ wherein Ph is a phenyl group and m and R' ar as hereinbefore defined. The reaction is typically carried out by lithiation of compound (VI) using, for example, n-butyl lithium in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) followed by reaction with the appropriate benzonitrile in a non-polar solvent, for example, cyclohexane.

Compounds of formula (IV) can also be prepared by reacting a comp und of formula (XVIII) as hereinbefore defined with sodium sulphide.

Compounds of formulae (V), (XIX), (VI) and $(R')_mPhCN$ as hereinbef re defined can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature. Thus compounds of formula (V) can be prepared from the corresponding 2-substituted 2-aminoethanols.

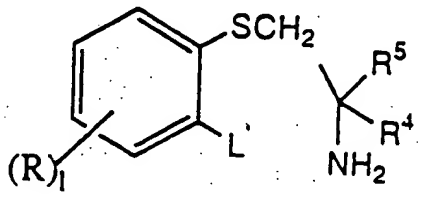
Compounds of formula (I) wherein n = 0 can also be prepared by cyclising a compound of formula (VIII)



(VIII)

wherein l, m, R, R', R^4 and R^5 are as hereinbefore defined and L' is halogen, for example, bromine, by treatment with strong base, for example, n-butyl lithium, in a suitable solvent, such as THF, at a low temperature, for example, -78°C.

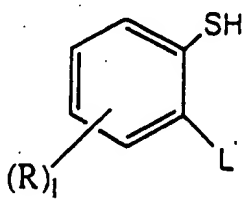
Compounds of formula (VIII) can be prepared by reaction of a compound of formula (IX)



(IX)

wherein l, L', R, R^4 and R^5 are as hereinbefore defined. with a compound of formula $(R')_m PhCHO$ wherein Ph is a phenyl group and m and R' are as hereinbefore defined. The reaction is typically carried out in a non-polar solvent, for example, toluene, in the presence of an acid, such as p-toluenesulphonic acid.

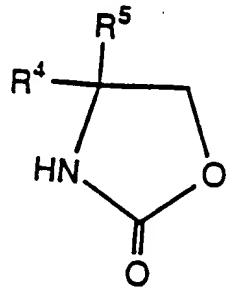
Compounds of formula (IX) can be prepared by reacting a compound of formula (XI)



(XI)

wherein l, L' and R ar as hereinbefore defined, with a compound of formula (V) wherein R^4 and R^5 are as hereinbefore defined, typically in a polar solvent, such as methanol.

Compounds of formula (IX) can also be prepared by reacting a comp und of formula (XI) as hereinbefore defined with a compound of formula (XVII)

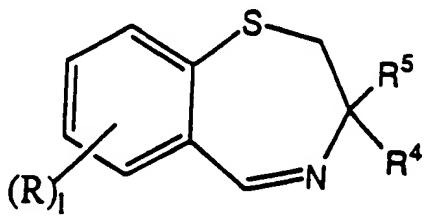


(XVII)

wherein R^4 and R^5 are as hereinbefore defined, in the presence of a Lewis acid, for example, lithium chloride, at an elevated temperature, such as 170-210°C.

Compounds of formulae $(R')_m PhCHO$ as hereinbefore defined, (XI) and (XVII) can be obtained commercially or prepared by methods known t those skilled in the art or obtainable from the chemical literature. Thus compounds of formula (XI) may be prepared from the corresponding disulphides and compounds of formula (XVII) from the corresponding 2-substituted 2-aminoethanols.

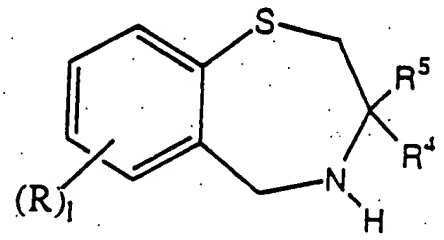
Compounds of formula (I) wherein n = 0 can also be obtained by phenylating a compound of formula (XIII)



(XIII)

wherein l, R, R^4 and R^5 are as hereinbefore defined, using, for example, an organometallic compound, such as $(R')_mPhLi$, $(R')_mPhCu$, $(R')_mPhZn$, or $(R')_mPhMgBr$ wherein Ph is a phenyl group and m and R' are as hereinbefore defined.

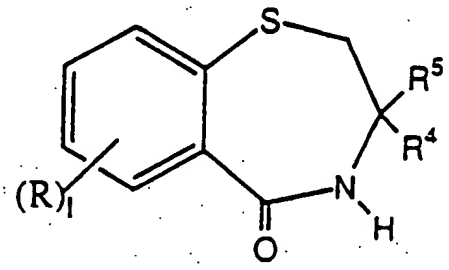
Compounds of formula (XIII) can be prepared by dehydrogenating the corresponding compound of formula (XIV)



(XIV)

wherein l, R, R^4 and R^5 are as hereinbefore defined, using, for example, an oxidising agent, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in a suitable solvent, for example, toluene.

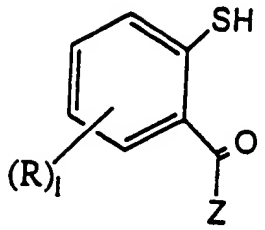
Compounds of formula (XIV) can be prepared by reducing the amide carbonyl group of the corresponding compound of formula (XV)



(XV)

wherein l, R, R^4 and R^5 are as hereinbefore defined, using, for example, lithium aluminium hydride.

Comp unds of f rmula (XV) can be prepared by reacting a mpound of formula (XVI)



(XVI)

wherein l and R are as hereinbefore defined and Z is C_{1-4} alkoxy, for example, methoxy, with a compound of formula (V) wherein R^4 and R^5 are as hereinbefore defined.

The compound of formula (XVI) wherein l = 0 can be prepared from commercially available 2,2'-dithiosalicyclic acid by methods known to those skilled in the art. Compounds of formula (XVI) wherein l ≠ 0 can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature.

Compounds of formula (I) wherein n = 1 or 2 can be prepared by oxidation of the corresponding compound of formula (I) wherein n = 0 or by oxidation of the corresponding compound of formula (III) wherein n = 0 prior to cyclisation and reduction to the compound of formula (I) using suitable oxidation conditions, for example, in the cas where n is to be 2, 30% aqu. H_2O_2 in the presence of trifluoroacetic acid.

Individual optical isomers of compounds of formula (I) substantially free, of other optical isomers can be obtained either by chiral synthesis, for example, by the use of the appropriate chiral starting material(s), such as the aziridine (V), or by resolution of the products obtained from achiral syntheses, for example, by chiral hplc.

Optional conversion of a compound of formula (I) to a c rr sponding acid addition salt may be effected by reaction with a solution of the appropriate acid. f r example, on f those recited earlier. Optional

conversion to a c rresponding base salt may be effected by reaction with a solution of the appropriate base, for example, sodium hydroxide. Optional conversion to a physiologically functi nal derivative, such as an ester, can be carried out by methods known to those skilled in the art or obtainable from the chemical literature.

For a better understanding of the invention, the following Examples are given by way of illustration and are not to be construed in any way as limiting the scope of the invention.

Synthetic Example 1

Preparation of (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

(a) Ethyl 2-aminobutyrate hydrochloride

A slurry of 2-aminobutyric acid (100g, Aldrich) in absolute ethanol (300ml) was stirred under nitrogen at 0°C and thionyl chloride (120.79g) was added dropwise. The reaction was stirred overnight at 0°C and then gradually warmed to room temperature. The resulting white slurry was heated under reflux for 3 hours, left to cool for 10 minutes, then poured into chilled diethyl ether (600ml) with hand stirring. The suspension was filtered and the solid product dried to give the desired product (150g) as a white solid. ^{1}H NMR consistent with proposed structure.

(b) Ethyl 2-benzylideneaminobutyrate

A solution of the product from step (a) (149.57g), magnesium sulphate (74.32g), and triethylamine (246ml) in dichloromethane (1500ml) was stirred at room temperature under nitrogen and benzaldehyde (94.91g, Aldrich) was added dropwise. The mixture was stirred at r m temperature for 3 hours then filtered. The filtrate was concentrated, triturated in diethyl ether, filtered

and concentrated to yield the desired product as a yellow il (174g). ^{1}H NMR consistent with the proposed structure.

(c) Ethyl 2-benzylideneamino-2-ethylhexanoate

Sodium hydride (32.49g, 60% dispersion in oil) and N,N-Dimethyl-formamide (DMF) (700ml) were stirred under nitrogen at ro m temperature and a solution of the product from (b) (178.13g) in DMF was added dropwise. After 2 hours stirring at r om temperature, a solution of butyl iodide (149.48g) in DMF was added dropwise and the reaction left stirring for a further 2 hours. The reaction was poured into an ice cold mixture of water (560ml), diethyl ether (300ml) and ammonium chloride (120g). The resulting organic layer was dried over potassium carbonate th n concentrated to give the desired product as a brown oil (220g).

(d) Ethyl 2-amino-2-ethylhexanoate

The product from (c) (233.02g) was partitioned between petroleum ether and 10% w/w hydrochloric acid (421ml) and stirred at r om temperature for 2 hours. The aqueous layer was extracted twice with petroleum ether and then chilled with ethyl acetate in an ice-salt bath. Sodium hydroxide pellets were added to the mixture until the aqueous layer was at pH 10. The latter was extracted twice with ethyl acetate and the combined ethyl acetate layers were dried over potassium carbonate, then concentrated and vacuum distilled to give the desired product as a colourless oil. ^{1}H NMR consistent with the proposed structure.

(e) 2-Amino-2-ethylhexan-1-ol

Lithium aluminium hydride (22.22g) was added to anhydrous diethyl ether (450ml) under nitrogen. The pr duct from (d) (129.0g) was diluted with diethyl ether (40ml) and added dropwise. The reaction was refluxed for 1 hour then co led to r om temperature.

1M sodium hydroxide (23ml) was added dropwis foll wed by deionised water. The resulting suspension was filtered and the filtrate concentrated to give the desired product as a colourless oil (87.9g). ^{1}H NMR consistent with the proposed structure.

(f) 2-Butyl-2-ethylaziridine

Acetonitrile (150ml) and the product from (e) (20.0g) were mixed under nitrogen, cooled to 2-3°C and chlorosulphonic acid (16.04g, Aldrich) was added dropwise keeping the temperature below 10°C. The coolant was removed and the slurry left to stir f r 80 minutes at room temperature. The reaction was concentrated in vacuo and co-distilled with water (50ml). 50% Aqueous s dium hydroxide (55.2g) and water (50ml) were added and the mixture was distilled at atomospheric pressure. The organic layer was collected from the distillate and dried with solid potassium hydroxide to give the desired product (12.8g). ^{1}H NMR consistent with proposed structure.

(g) 2-Thiobenzophenone

A solution of N,N,N',N'-tetramethylethylenediamine (TMEDA) (104.6g) in cyclohexane (500ml) was cooled and 2.5M n-butyl lithium (360ml) was added. A solution of thiophenol (50.0g) in cyclohexane (100ml) was added slowly to the butyl lithium solution and the reaction was stirred at room temperature overnight. Benzonitrile (46.4g, Aldrich) in cyclohexane (100ml) was added to give a slurry which was stirred overnight at r m temperature. Water (500ml) was added and the mixture stirred for 30 minutes then the aqueous layer was separated and treated with solid sodium hydroxide to give pH 14. The solution was boil d for 90 minutes, cooled to room temperature and acidified to pH 1-2 with conc. HCl. The acidic solution was extracted with dichl romethane and the combined extracts dried. then concentrated to give a red oil. The oil was treated with 1M aqu.

NaOH, extracted with dichloromethane and the aqueous layer separated and treated with conc. HCl acid to give an oil. The oil was extracted into dichloromethane and the combined extracts dried, then concentrated to give the desired product as an orange-red oil (83.4g). ^1H NMR consistent with proposed structure.

(h) 2-(2-Amino-2-ethylhexylthio)benzophenone

The product from (g) was dissolved in methanol (to a total volume of 250ml) and an equimolar amount of the product from (f) in methanol (total volume 120ml) was added over 20 minutes. The mixture was stirred at room temperature for 75 minutes then concentrated in vacuo to give a dark red oil. This oil was taken up in diethyl ether (400ml) and filtered to remove contaminating solids. The desired product was left as a solution in ether f r use in (i). ^1H NMR consistent with proposed structure.

(i) 3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

1M Ethereal hydrochloric acid (275ml) was added to a solution of the product from (h) (85.0g) in diethyl ether and the mixture was concentrated in vacuo. The residue was azeotropically distilled by addition of 2,6-lutidine (175ml) and refluxing in a Dean-Stark apparatus overnight. The mixture was concentrated in vacuo, neutralised by addition of 5% sodium bicarbonate then the minimum volume of ethyl acetate was added to dissolve the red oil. The organic layer was separated, washed with brine, dried and concentrated. The crude residue was purified by column chromatography on silica using toluene as eluant. Concentration of the relevant fractions gave the desired product (63.7g). ^1H NMR consistent with the proposed structure.

(j) (+-)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine

1M Diborane (211ml in THF) was added over 45 minutes to a solution of the product from (i) (63.7g) in THF under nitrogen. Reaction was stirred at room temperature for 17 hours. 50% Hydrochloric acid (125ml) was added and the mixture was concentrated in vacuo. The residue was partitioned between aqu. NaOH and ethyl acetate. The organic layer was dried and concentrated to give an orange-yellow oil (67.5g) comprising cis and trans isomers which was chromatographed on silica using toluene as eluant to give the desired product as a pale yellow oil (27.3g). ^{1}H NMR consistent with the proposed structure.

(k) (+-)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

30% Aqueous hydrogen peroxide (73.1g) and trifluoroacetic acid (TFA) (225ml) were cooled and a solution of the product from (j) (70.0g) in TFA (200ml) was added. The reaction was stirred at room temperature for 24 hours, then added to water (1000ml) and basified with solid sodium hydroxide. The resulting insoluble solid was filtered off, warmed with 1M aqu. NaOH and extracted into ethyl acetate. The combined extracts were evaporated in vacuo to give the desired product (69.0g). ^{1}H NMR consistent with the proposed structure.

(l) (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

The product from (k) (208.3g) was mixed with diethyl ether (1500ml) and (-)-di-p-toluoyl-L-tartaric acid (225.2g, Schweitzerhall) in diethyl ether added. On standing, a white solid precipitated which was filtered off and recrystallised from acetone/hexane t give the desired product as the acid salt. The

titl compound was liberated from its salt by treatment with 1M aqu. NaOH and extracted with ethyl acetate. The combined extracts were evaporated in vacuo to give the desired product as a white solid (83.0g), mp 115-116°C.

Analysis: Calcd. C 70.55; H 7.61; N 3.92; S 8.97
Found: C 70.58; H 7.56; N 3.96; S 8.88

^{1}H NMR (DMSO-d_6), δ: 0.81-0.92 (6H, m, 2xCH_3); 1.15-1.40 (4H, m, 2xCH_2); 1.47-1.70 (3H, m, CH_2 + NH); 1.80-1.90 (1H, m, CH_2); 2.13-2.24 (1H, m, CH_2); 3.07-3.46 (2H, q, CH_2SO_2); 6.09 (1H, s, CH); 6.71-6.74 (1H, m, Ar-H); 7.26-7.41 (7H, m, Ar-H); 8.10-8.13 (1H, m, Ar-H)

Alternative preparation of (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

(a) Ethyl 2-aminobutyrate hydrochloride

Thionyl chloride (1.25 moles) was added to a solution f 2-aminobutyric acid (1 mole) in SD12A3 (95% ethanol/5% toluene) at a temperature of <5°C. When addition was complete, the mixture was stirred at 27°C for 16 hours and the resulting precipitate filtered off and washed with methyl t-butyl ether t give the desired product as a white solid (97% yield).

(b) Ethyl 2-benzylideneaminobutyrate

Triethylamine (2 moles) was added to a solution of the product from step (a) (1 mole) in toluene. When addition was complete, benzaldehyde (1 mole) was added. The mixture was azeotrop d until no further water was collected, then cooled to ro m temperature and filtered. The filtrate was evaporated in vacu t give the desired product as an oil.

(c) Ethyl 2-benzylideneamino-2-ethylhexanoate

A 1.6M solution of n-butyl lithium in hexane (33 mmoles, Aldrich) was added to a solution of diisopropylamine (40 mmoles) in THF (21ml) at a temperature of 5-10°C. When addition was complete, the mixture was added to a solution of the product from step (b) (30 mmoles) in THF (20ml) at a temperature of 5-10°C. When addition was complete, n-butyl iodide (40 mmoles) was added and the mixture allowed to warm to room temperature. After 20 hours, the mixture was poured into water/diethyl ether (1.1L/0.5L) and the organic layer separated, washed with brine (1.1L), dried and evaporated in vacuo to give the desired product as an amber liquid (100% yield).

(d) Ethyl 2-amino-2-ethylhexanoate

A solution of the product from step (c) (1 mole) in 1N aqu. HCl (1.2 moles) was stirred for 10 minutes at room temperature, then washed with toluene. The pH of the remaining aqueous phase was adjusted to 7 using 12.5% w/v sodium hydroxide, then cooled to 10°C, further basified to pH 12 and extracted with toluene. The extracts were combined, washed with brine, dried and evaporated in vacuo. The residue was distilled to give the desired product as an oil (70-80% yield).

(e) (R)-2-Amino-2-ethylhexanoic acid

A suspension of pig liver esterase (0.1g, Sigma-Aldrich-Fluka) in water was added to an aqueous solution of the product from step (d) (100g). When addition was complete, the pH of the mixture was adjusted to 9.7 using 1N aqu. NaOH and maintained at this value by the addition of further 1N aqu. NaOH. After the addition of a predetermined amount of 1N aqu. NaOH (85g over 10 hours), the mixture was washed with diethyl ether to rem ve unreacted (S)-ethyl 2-amin -2-ethyl-hexanoate. The remaining

aqueous phase was evaporated in vacuo to give a white solid comprising the desired product and its sodium salt (40-45% yield).

(f) (R)-2-Amino-2-ethylhexan-1-ol

The product from step (e) (20g) was added to a 1M solution of lithium aluminium hydride (1.5 molar equivalents) in THF and the mixture refluxed for 3 hours, then stirred for 16 hours at room temperature. The mixture was cooled to about 0°C, then quenched with water and 1N aqu. NaOH added. The resulting solid was broken up with additional water and the suspension heated at 50°C for 5 minutes, then cooled to room temperature, diethyl ether (100ml) added and filtered. The filtrate was evaporated in vacuo to give the desired product as an oil (82% yield).

(g) (R)-2-Butyl-2-ethylaziridine

Chlorosulphonic acid (1 molar equivalent) was added to a solution of the product from step (f) (15g) in dichloroethane (90ml) at a temperature of <16°C. When addition was complete, the mixture was stirred for 2 hours at room temperature and then evaporated in vacuo. Water (60ml) and 50% w/v aqu. NaOH (41ml) were added and the mixture distilled at atmospheric pressure. The organic phase of the distillate was separated and dried over KOH to give a solution of the desired product (77% yield).

(h) 2-Thiobenzophenone

A 2.5M solution of n-butyl lithium (2 moles) in hexane was added to a solution of N,N,N',N'-tetramethylethylenediamine (TMEDA, 2 moles) in cyclohexane at a temperature of -8 to 0°C. When additi n was c mplete, a 4.5M soluti n f thi phen l (1 mole) in cycl hexane was added and the temperature all wed to rise to 40-50°C. When addition was complete, th mixtur was stirred

overnight at room temperature. A 4.5M solution of benzonitrile (1 mole) in cyclohexane was then added over 1 hour at a temperature of 15-20°C. When addition was complete, the mixture was heated at 40°C for 4 hours, then stirred at room temperature for 72 hours and quenched with water. The resulting organic phase was extracted with 1N sodium hydroxide and the combined extracts heated at 75°C for 2.5 hours, then cooled to room temperature, acidified to pH 1 using conc. HCl and extracted four times with toluene. The combined extracts were dried and evaporated in vacuo to give a red oil which was taken up in SD3A and stirred at room temperature for 16 hours. The resulting precipitate was filtered off and washed with SD3A to give the desired product as a white solid (61% yield).

(i) (R)-3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

The solution from step (g) (1.05 moles) was added to a suspension of the product from step (h) (1 mole) in 2,6-lutidine (50ml) at a temperature of about 25°C. When addition was complete, the mixture was stirred at room temperature for 1.5 hours, then conc. HCl (6.3ml) added. When addition was complete, the mixture was azeotroped for 3 hours, then stirred at room temperature overnight and evaporated in vacuo. The residue was taken up in 5% w/v aqu. $NaHCO_3$ and the solution extracted twice with ethyl acetate. The combined extracts were washed with brine, dried and evaporated in vacuo. The residue was chromatographed in silica gel using 95:5 hexane:ethyl acetate as eluant to give the desired product as a red-orange oil (77% yield).

(j) (RR,RS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine

A 1M solution of diborane in THF (63ml) was added to a solution of the product from step (i) (0.9 molar equivalents) in THF (100ml) at a temperature of about 1°C. When addition was

overnight at room temperature. A 4.5M solution of benzonitrile (1 mole) in cyclohexane was then added over 1 hour at a temperature of 15-20°C. When addition was complete, the mixture was heated at 40°C for 4 hours, then stirred at room temperature for 72 hours and quenched with water. The resulting organic phase was extracted with 1N sodium hydroxide and the combined extracts heated at 75°C for 2.5 hours, then cooled to r om temperature, acidified to pH 1 using conc. HCl and extracted four times with toluene. The combined extracts were dried and evaporated in vacuo to give a red oil which was taken up in SD3A and stirred at room temperature for 16 hours. The resulting precipitate was filtered off and washed with SD3A to give the desired product as a white solid (61% yield).

(i) (R)-3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

The solution from step (g) (1.05 moles) was added to a suspension of the product from step (h) (1 mole) in 2,6-lutidine (50ml) at a temperature of about 25°C. When addition was complete, the mixture was stirred at room temperature for 1.5 hours, then conc. HCl (6.3ml) added. When addition was complete, the mixture was azeotroped for 3 hours, then stirred at room temperature overnight and evaporated in vacuo. The residue was taken up in 5% w/v aqu. $NaHCO_3$ and the solution extracted twice with ethyl acetate. The combined extracts were washed with brine, dried and evaporated in vacuo. The residue was chromatographed in silica gel using 95:5 hexane:ethyl acetate as eluant to give the desired product as a red-orange oil (77% yield).

(j) (RR,RS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine

A 1M solution of diborane in THF (63ml) was added to a solution of the product from step (i) (0.9 molar equivalents) in THF (100ml) at a temperature of about 1°C. When addition was

complete, the mixture was stirred overnight at room temperature, then cooled to about 0°C and 50% v/v HCl (40ml) added. When addition was complete, the mixture was stirred at room temperature for 1 hour, then concentrated in vacuo to remove the THF. Water (25ml) was added to the remaining aqueous phase, the pH adjusted to 8 using 12% w/v aqu. NaOH and the solution extracted with ethyl acetate. The combined extracts were dried and evaporated in vacuo to give the desired product as a red-orange oil comprising cis and trans isomers (100% yield).

(k) (RR,RS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

A suspension of the product from step (j) (0.33 molar equivalents) in trifluoroacetic acid (25ml) was added to a solution of 30% aqu. H_2O_2 (10.2ml) in trifluoroacetic acid (20ml) at a temperature of about 0°C. When addition was complete, the mixture was stirred overnight at room temperature, then poured into water (200ml) to give a waxy solid which was separated and taken up in 1N aqu. NaOH. The solution was heated to 40°C, then cooled and extracted with ethyl acetate. The combined extracts were washed with 1N aqu. NaOH, dried and evaporated in vacuo to give an oil comprising the cis and trans isomers (84% yield).

(l) (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

A solution of (-)-di-p-toluoyl-L-tartaric acid (1 mole) in diethyl ether (20ml) was added to a solution of the product fr m step (k) (1 mole) in diethyl ether (20ml). When addition was complete, the mixture was stirred at room temperature for 2 hours and the resulting crystals filtered off, washed with diethyl ether and dried to give the (RR)-tartrate salt which was neutralised with 1N aqu. NaOH and extracted with ethyl acetate. Th combined extracts were dried and evaporated in vacuo to give

an oil which crystallised fr m hot hexanes to give the desired product as a white solid (58% yield). The mp, elemental analysis and ^{1}H NMR of the product were in agreement with those obtained by the alternative synthesis.

Preparation of (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride

The product from Synthetic Example 1 (0.95g) was taken up in ether (75ml), 10M ethereal HCl (50ml) added and the mixture stood for 3 hours. The resulting precipitate was filtered off and dried to give the desired product as a white solid (0.86g), mp 184-188°C.

Analysis: Calcd. C 64.02; H 7.16; N 3.56; S 8.14
Found: C 64.09; H 7.16; N 3.01; S 8.21

^{1}H NMR (DMSO-d_6), δ: 0.81-0.91 (6H, m, CH_3); 1.00-1.04 (1H, m, CH_2); 1.29 (3H, b, CH_2); 1.92-2.00 (3H, b, CH_2); 2.50-2.51 (3H, b, CH_2 + $\overset{+}{N}H_2$); 3.40-4.80 (4H, b, CH_2SO_2); 6.20 (1H, b, CH); 6.83 (1H, b, Ar-H); 7.56-7.70 (7H, b, Ar-H); 8.10 (1H, b, Ar-H)

Synthetic Examples 2 - 64

Each of the following compounds of formula (I) was prepared by a method analogous to that of Synthetic Example 1 or by one of the other synthetic routes described herein. In all cases, ^{1}H NMR and elemental analysis were consistent with the proposed structure.

2) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 98-100°C;

3) (-)-Trans-3-Methyl-3-propyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benz thiazepine 1,1-dioxide, mp 129-130°C;

4) 3-Ethyl-3-methyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine, mp 124-125°C;

5) (+)-3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 100-102°C;

6) 3-Butyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 103-104°C;

7) 3-Methyl-3-propyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 120-121°C;

8) 3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 115-116°C;

9) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 101°C;

10) (+)-Trans-2,3,4,5-Tetrahydro-3-methyl-5-phenyl-3-propyl-1,4-benzothiazepine 1,1-dioxide, mp 129-130°C;

11) (-)-3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin 1,1-dioxide, mp 101-103°C;

12) 3-Ethyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine, mp 110-112°C;

13) 3-Ethyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine hydrochloride $0.25H_2O$, mp 162-164°C (eff.);

14) 3-Ethyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 128-129°C;

15) 3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine hydr chloride, mp 211-214°C;

16) (+-)-2,3,4,5-Tetrahydro-3-methyl-5-phenyl-3-propyl-1,4-benzothiazepine, mp 101-103°C;

17) 2,3,4,5-Tetrahydro-3-methyl-5-phenyl-3-propyl-1,4-benzothiazepine, mp 72-74°C;

18) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine hydrochloride $0.25H_2O$, mp 205-207°C;

19) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine 1,1-dioxide $0.25H_2O$, mp 115-118°C;

20) 2,3,4,5-Tetrahydro-5-phenyl-3,3-dipropyl-1,4-benzothiazepine hydrochloride, 209-211°C;

21) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine 1,1-dioxide hydrochloride $0.33H_2O$, 206-209°C;

22) 2,3,4,5-Tetrahydro-5-phenyl-3,3-dipropyl-1,4-benzothiazepine 1,1-dioxide, mp 104-106°C;

23) 3,3-Dibutyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine hydrochloride, mp 209-212°C;

24) 3-Butyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine hydrochloride, mp 203-205°C;

25) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine hydrochloride, mp 205-207°C;

26) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 209-212°C;

27) 2,3,4,5-Tetrahydro-3-methyl-3-pentyl-5-phenyl-1,4-benzothiazepine maleate, mp 182-183°C;

28) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine hydrochloride, mp 198-200°C;

29) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 138-140°C;

30) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine, light yellow oil;

31) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine, light yellow oil;

32) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 113-115°C;

33) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine 1-oxide, mp 103-105°C;

34) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 199-201°C;

35) (+-)-Trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-1.4-benzothiazepine 1-oxide, mp 98-101°C;

36) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1-oxide, mp 133-136°C;

37) (+-)-Cis-7-Chloro-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 0.4 toluene, light yellow oil;

38) (+-)-Trans-7-Chloro-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 0.3 toluene, light yellow oil;

39) (+-)-Trans-3-Butyl-7-Chloro-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1.4-benz thiazepine 1.1-dioxide, mp 100-102 C;

40) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 194-196°C;

41) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-tolyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 204-206°C;

42) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-tolyl)-1,4-benzothiazepine 1,1-dioxide, mp 155-156C;

43) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,4-benzothiazepine, mp 75-77°C;

44) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 109-111°C;

45) (+-)-Cis-3-Butyl-3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepine, mp 76-78°C;

46) (+-)-Trans-3-Butyl-5-(3,4-dichlorophenyl)-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, mp 98-100°C;

47) (+-)-Trans-3-Butyl-5-(4-chlorophenyl)-3-ethyl-2,3,4,5-tetrahydr - 1,4-benzothiazepine 1,1-dioxide hydrochloride 0.3 H_2O, mp 178-180°C;

48) (+-)-Cis-3-Butyl-5-(4-chlorophenyl)-5-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 186-188°C;

49) Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 139-142°C;

50) Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-nitrophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 139-142°C;

51) (+-)-Trans-5-(4-Benzyloxyphenyl)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide, mp 94-95°C;

52) (+-)-Cis-5-(4-Benzyloxyphenyl)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide, mp 137-138°C;

53) (+-)-Trans-5-(4-Benzyloxyphenyl)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, mp 97-98°C;

54) (+-)-Trans-3-[4-(3-Butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-5-yl)phenoxy]propanesulphonic acid 1,1-dioxid , mp 270°C (dec.);

55) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(2-fluorophenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 194-196°C;

56) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-fluorophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 143-145°C;

57) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-pyridyl)-1,4-benzothiazepine 1,1-dioxide, mp 121-123°C;

58) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-pyridyl)-1,4-benzothiazepine 1,1-dioxide, mp 110-111°C;

59) (+-)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-trifluoromethylphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 64-65°C;

60) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-trifluoromethylphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 110-112°C;

61) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3,4-difluorophenyl)-1,4-benz thiazepine 1,1-dioxide, mp 205-215°C;

62) (+-)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(2,4-difluoro-phenyl)-1,4-benzothiazepine 1,1-dioxide, mp 97-99°C;

63) (+-)-Trans-3-isopentyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 86-87°C; and

64) (+-)-Cis-3-isopentyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 123-125°C.

Pharmaceutical Composition Examples

In the following Examples, the active compound can be any compound of formula (I) and/or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The active compound is preferably (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine or one of the compounds of Synthetic Examples 2 to 64.

(i) Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Sodium Starch Glycollate	20	12
(d)	Povidone B.P.	15	9
(e)	Magnesium Stearate	5	3
		500	300

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250

(b)	Lact se 150	150	-
(c)	Avicel PH 101	60	26
(d)	Sodium Starch Glycollate	20	12
(e)	Povidone B.P.	15	9
(f)	Magnesium Stearate	5	3
		500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in composition E is of the direct compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

Composition F (Controlled release c mpositi n)

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium Stearate	7
		700

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity f polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellul se acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L,

these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B

	mg/capsule
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2
	420

Composition C

	mg/capsule
(a) Active ingredient	250
(b) Macrogol 4000 BP	350
	600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Ethyl Cellulose	13
		513

The controlled release capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Cellul se Acetate Phthalate	50
(e)	Diethyl Phthalate	5
		555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition

Active ingredient		0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0)	to	10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition

Active ingredient		0.20 g
Benzyl Alcoh l		0.10 g
Glycofurol 75		1.45 g
Water f r Injection	q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient		0.25g
Sorbitol Solution		1.50g
Glycerol		1.00g
Sodium Benzoate		0.005g
Flavour		0.0125ml
Purified Water	q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

	mg/suppository
Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200μm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250μm stainless steel screen and, with continuous stirring, allowed to cool to 40 C. At a temperature of 38-40°C. 2.02g aliquots f the mixture are filled int

suitable plastic moulds and the suppositories allowed to cool to r om temperature.

(vii) Pessary composition

	mg/pessary
Active ingredient (63μm)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

(viii) Transdermal composition

Active ingredient	200mg
Alcohol USP	0.1ml
Hydroxyethyl cellulose	

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm^2.

Biological Assay

In vitro inhibition of bile acid uptake

Freshly prepared rat distal ileal brush border membrane vesicl s (about 200mg vesicle protein) were incubated for 30 seconds at 24°C in an incubation mixture comprising 10μM ^3H taurocholate, 100mM NaCl (or KCl) and 80mM mannitol in 20mM Hepes Tris pH 7.4. Each test compound was diss lved in than l (or water) and then diluted with incubati n mixture to an ethanol concentration of not m re than 1% v/v. The

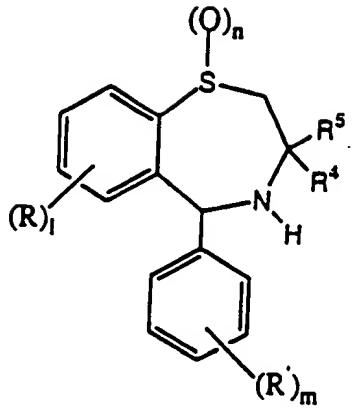
incubation was terminated by rapid dilution and filtration and the filter washed with an ice-cold isotonic sodium-free buffer.

The uptake of ^{3}H taurocholate was measured by the radioactivity remaining on the filter and converted to pmoles/mg vesicle protein. The active, ie sodium-dependent, uptake was obtained by subtracting the passive uptake measured in 100mM KCl from the total uptake measured in 100mM NaCl. The active uptake for each test compound was compared with a control active uptake and the results expressed at % inhibition of bile acid uptake.

For the compound of Synthetic Example 1, the % inhibition of bile acid uptake at concentrations of 10, 3, 1 and 0.3μM was 96, 85, 69 and 55% respectively.

CLAIMS

1. A compound of formula (I)



(I)

wherein

l is an integer of from 0 to 4;

m is an integer of from 0 to 5;

n is an integer of from 0 to 2;

R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^4 is a C_{1-6} straight alkyl group; and

R^5 is a C_{2-6} straight alkyl group;

and salts, solvates and physiologically functional derivatives thereof.

2. A compound of formula (I) as claimed in Claim 1, wherein

n is 2;

R^4 is methyl, ethyl, n-propyl, or n-butyl; and

R^5 is ethyl, n-propyl, or n-butyl;

and salts, solvates and physiologically functional derivatives thereof.

3. A compound of formula (I) as claimed in Claim 2, which compound is in the trans configuration as herein defined, or a salt, solvate, or physiologically functional derivative thereof.

4. A compound of formula (I) as claimed in Claim 3, which compound is trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, or a salt, solvate, or physiologically functional derivative thereof.

5. The compound of formula (I) claimed in Claim 4, which compound is in the (RR)-, (SS)-, or (RR,SS)-form, or is a salt, solvate, r physiologically functional derivative of any thereof.

6. (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide or a salt, solvate, or physiologically functional derivative thereof.

7. (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

8. (+-)-(RR,SS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide or a salt, solvate, r physiologically functional thereof.

9. (+-)-(RR,SS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

10. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use as a therapeutic agent.

11. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of a clinical condition for which a bile acid absorption inhibitor is indicated.

12. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of hyperlipidaemia.

13. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of atherosclerosis.

14. Use of a compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of a clinical condition for which a bile acid absorption inhibitor is indicated.

15. Use of a compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of hyperlipidaemia.

16. Us of a compound as claimed in any of Claims 1 t 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of atherosclerosis.

17. A method for the prophylaxis or treatment of a clinical conditi n in a mammal for which a bile acid absorption inhibitor is indicated which comprises the administration to said mammal of an effective bile acid absorption inhibiting amount of a compound of formula (I) as claimed in any of Claims 1 to 7 or of a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

18. A method as claimed in Claim 15 for the prophylaxis or treatment of hyperlipidaemia.

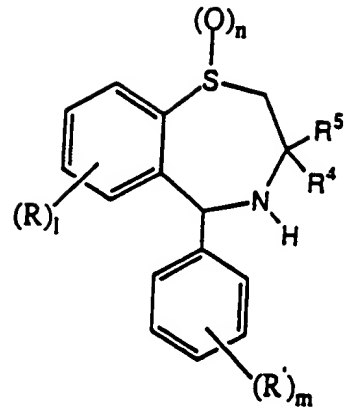
19. A method as claimed in Claim 15 or 16 for the prophylaxis or treatment of atherosclerosis.

20. A method as claimed in any of Claims 15 to 17 wherein said mammal is a human.

21. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of Claims 1 to 7 or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

22. A pharmaceutical composition as claimed in Claim 19 which is in the form of a tablet or capsule.

23. A process for the preparati n f a c mp und of formula (I)



(I)

wherein

l is an integer of from 0 to 4;

m is an integer of from 0 to 5;

n is an integer of from 0 to 2;

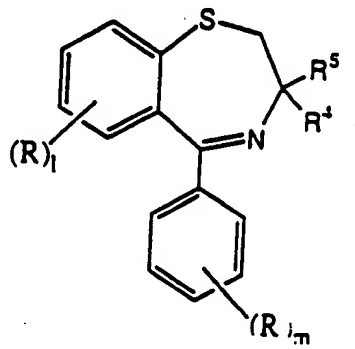
R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^4 is a C_{1-6} straight alkyl group; and

R^5 is a C_{2-6} straight alkyl group;

which comprises

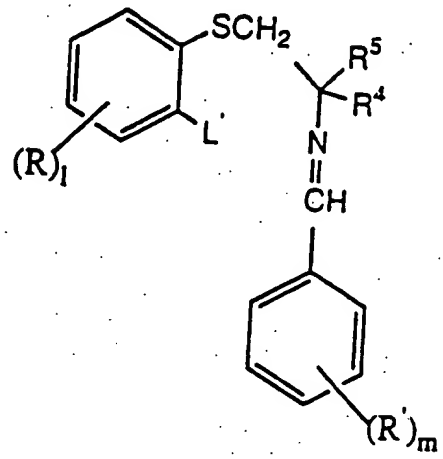
(a) reducing the imine bond of a compound of formula (II)



(II)

wherein l, m, R, R', R^4 and R^5 are as hereinbefore defined;

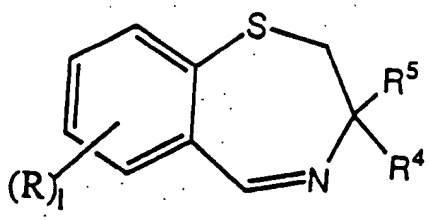
(b) cyclising a compound of formula (VIII)



(VIII)

wherein l, m, R, R', R^4 and R^5 are as hereinbefore defined and L' is halogen; or

(c) phenylating a compound of formula (XIII)



(XIII)

wherein l, R, R^4 and R^5 are as hereinbefore defined;

and optionally oxidising the compound of formula (I) so obtained to the corresponding compound wherein n = 1 or 2 followed by optional conversion to a salt, solvate, r physiologically functional derivative thereof.

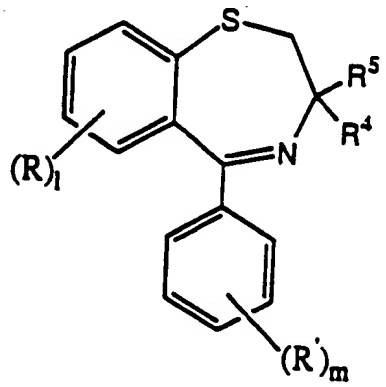
24. A method f preparing a pharmaceutical composition which comprises

(a) preparing a compound of formula (I) or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof by a process as claimed in Claim 21; and

(b) admixing the product from step (a) with at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

25. A method as claimed in Claim 22 which comprises an additi nal step (c) wherein the admixture from step (b) is formed int a tablet or capsule.

26. A compound of formula (II)



(II)

wherein l, m, R, R', R^4 and R^5 are as defined in Claim 1.

27. 3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

28. (R)-3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D281/10

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,3 362 962 (EARL R. NUTLEY ET AL.) 9 January 1968 cited in the application see the whole document	1,2, 10-16

[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

V. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 APRIL 1993	13. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	FRANCOIS J.C.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9300328
SA 70210

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/04/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3362962		BE-A- 658798	26-07-65
		CH-A- 494207	31-07-70
		DE-A- 1545932	08-01-70
		FR-M- 4916	
		FR-A- 1422569	
		GB-A- 1091182	
		NL-A- 6500817	26-07-65
		US-A- 3503985	31-03-70
		US-A- 3523974	11-08-70
		US-A- 3530139	22-09-70
		US-A- 3631089	28-12-71

FORM P0479